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of the Society held at

Manson House, 26, Portland Place, London W,

on

Thursday, 18th November, 1943, at 3 p.m

THE PRESIDENT

SIR H HAROLD SCOTT K.C.M.G. M.D. F.R.C.P., F.R.S.E.,

in the Chair

PAPER

A SURVEY OF TROPICAL DISEASES AS SEEN IN THE MIDDLE EAST

BY

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INTRODUCTION

From March 1941 to February 1943 I was in charge of the Medical Division of a hospital in Egypt By the piped distribution of purified water a camp had been laid out in this desert to hold about 100 000 troops served by a group of large hospitals Troops were always coming and going some newly landed a few going home, reinforcements being hurried to and from the Western Desert, battle-worn troops from operational fronts, resting and re-equipping There was a steady flow of local sick and an equal number of admissions from forward medical units by hospital train. The patients were chiefly of British stock but a native section of 48 beds gave some opportunity of seeing non indigenous tropical diseases

We worked at high pressure and my Division treated 17 000 patients in 2 years yet the sickness rate was low and the average beds occupied by

sick and wounded was but 8 per cent of the Force a small figure when is realised that few could be "sick in quarters" and there were no C Reception hospitals the proportion of medical to surgical admissions to hospital was three to two, a low figure As we were not a specialist [illegible] our patients were unselected admissions, and my figures are probably a sample of the disease incidence in Egypt and Libya.

Our object was not research the laboratory staff was small, and o overtaxed even by routine work there was usually a shortage of med officers, and each had 100 to 140 beds our sole duties were the rapid res of men to fighting fitness, or the relegation of the subnormal to an a priate category and their unnecessary retention meant a serious d of the scanty reserves the climate was not a stimulating one, and we all the well-known lethargy of our neighbours, the fellaheen. Perhaps this explain the pitifully few garnerings from our wealth of opportunity

Working conditions.

The hospital had 1,200 beds, in a crisis expanded to 1,500 three-qu were in marquees or small tents (E.P.L.P.) for isolation, the rest in Ni or wattle and daub huts. The site was sandy gravel there were few days and the winters were not cold, so that the conditions were well to the climate and the main discomforts were winds, heat and sandst In the second year electricity was installed throughout and replaced hur lamps in wards and living quarters hot water was available from cist heated by steam centrally generated conservancy was by deep trench latrin and, for infected stools, Otway pits. Diet drugs and equipment were same as in a military hospital in England or the B.E.F., but at times sh losses caused difficulties in supplies.

Excellent canteens, and a good cinema were provided, and convales depots were available and freely used.

Training of Medical Officers

I was impressed by the high standard of knowledge, the sound ground in general principles, the keenness and the adaptability to strange and new diseases of the numerous British and Dominion medical officer had under me

Nevertheless for military purposes there is room for improvement F medical officer has a 2 weeks' course of tropical medicine before abroad and this cannot be modified for those going to India or West A or the Middle East. As a supplement to such academic instruction a weeks training in the medical wards of a military hospital abroad invaluable. The hospital staffs are familiar with local problems, but all frequently the early treatment of acute tropical diseases was in the hand medical officers newly arrived in the country unfamiliar with its or their treatment, and in the fighting zones quite inaccessible to skilled

This could be corrected by the posting of each new medical officer to a Military hospital in permanent or temporary exchange for a trained medical officer from the hospital. Two weeks posting to the Medical Division of a hospital each year would also help to keep the field force medical officer up to date, and to give him the clinical opportunities which he lacks but is keen to have

Higher authorities are fully aware of the desirability of such local training but it is seldom practicable under conditions of modern warfare.

Tropical Diseases

Seventeen thousand odd medical cases passed through the hospital during the 22 months it was working in Egypt, and I have analyzed 13,500 consecutive admissions for the first 18 months the remaining 3,500 cases in the last 4 months are comparable 45 per cent. of medical admissions were for tropical diseases and if desert sores be included the figure would be about 50 per cent.

Table I

6 144 cases of tropical diseases

Dysentery Group	4 178	68 per cent.	99 per cent.
Short term fevers	1 153	19 "	
Malaria	735	12 "	
Avitaminosis	34		1 per cent.
Relapsing fever	19		
Bilharziasis	18		
Kala-azar	6		
Leprosy	1		
Effects of heat	1		

Ignoring the interesting but unimportant 1 per cent., two-thirds of the tropical cases were admitted for acute diarrhoea, and one-third for pyrexia with possibly splenomegaly These 6 000 soldiers were in hospital for 2 to 3 weeks with often another week at a convalescent depot

The incidence of the non-tropical group of diseases was similar to what is found in England with one notable difference the low admission rate for chronic dyspepsia of 4 per cent

If selected and fit men are sent to the Middle East they suffer from the same diseases and probably to the same extent as in England, but hospital admissions would be doubled because of the occurrence of acute diarrhoea malaria and sandfly fever

Acute Diarrhoea.

Probably every soldier in the M.E.F had at least one attack of acute diarrhoea usually soon after arrival some considerable degree of immunity

must have been acquired and the rarity of acute diarrhoea in our sec summer was the subject of comment, although new troops in the area w badly affected. Not all cases of diarrhoea were admitted to hospital, Major J. H. L. Easton *from a study of the books in the M.I. rooms* in district thought that only about 6 per cent. of those reporting sick were to hospital.

The seasonal incidence of diarrhoea is well known, although hospital ad ion varied according to the fullness of the camp: the winter months p duced few cases while there were peaks in early and late summer—the d in numbers in high summer being associated with fewer flies.

An instructive military lesson was supplied when powerful reinfo arrived in the critical August of 1942: part of a famous division arrived war area after a quick voyage from the United Kingdom and the subseq story of the Division leaves no doubt about their fitness, toughness and d cipline. Yet had they by force of circumstances been forced to fight w the first few weeks of their arrival, I should doubt their ability to have so *and this would apply to any troops landing at that season in Egypt.* O hospital was flooded with cases of acute diarrhoea, in 1 day ninety new were admitted, and I had 450 beds occupied by dysentery cases for a time. One battalion alone had 350 men in hospital during a period of 3 and in 1 day 180 of them were warded with diarrhoea. Clearly the a were greater than usual, and many more than 6 per cent. were admi perhaps owing to the inexperience of the unit medical officers. Unsea troops would have difficulty in pursuing an invasion of such a country such a season, salted troops could however succeed—during the period o own unit was almost free from dysentery.

I cannot add anything but impressions to the reasons for the spread diarrhoea. In any military community and in any climate, brief attacks mild diarrhoea keep on recurring—I have seen this in England and in Fran *Whilst in Egypt* throughout all seasons this inconvenient diarrhoea kept in our wards perhaps once a week, and quite eluded all attempts at s it appears to be a mild food poisoning and not dysenteric. The more dysenteric outbreaks are probably spread by the "dust of dried dejecta" the "repulsive regurgitations, dangerous droppings and filthy feet of fae feeding flies fouling food."

Its incidence was very low when flies disappeared in the winter and in extremely hot midsummer weeks: whilst it was common experience that disease was always worst in the field when enemy territory with its neg sanitation was occupied. The dysentery rate bore a relation to camp hygi and anti-fly measures, yet the disease has never yet been controlled in w and that our hospital should admit an average of sixty cases a week for months shows how unsatisfactory the position is.

I am unable to my lasting regret to tell you about the problem as

by the medical officer in the field of operations as I was not sent forward. I deplored the lack of uniformity in treatment as described in the Field Medical Cards of patients reaching us—salts or castor oil, alternating with chalk and opium or opium pills were favourite combinations of pharmacological incompatibles. The forward units lacked specific drugs but many medical officers lacked practical knowledge of how to manage dysentery cases as they had not had the advantage of training in a base hospital. Had the special knowledge *and judgment* of an officer who had had charge of dysentery wards been available in the field with a supply of specific drugs a large number of men would have been retained in the line—indeed many men were quite cured *when they* reached us—and a standard method of early treatment might have been established.

DYSENTERY AS SEEN IN A MILITARY HOSPITAL.

Apart from our trivial and recurrent ward outbreaks of mild food poisoning, which I dismiss, minor diarrhoea and true dysentery were to us the same disease. Every gradation of severity was seen in affected units at the same time. Why ascribe the mild "gyppy tummy" to the ingestion of sand or a draught on the abdomen at night or some other curious theory and incriminate the dysentery bacillus for the severer forms? The selective media now available should establish the clinically irresistible conclusion that they are the same disease. We did not have them; the pathologist would only culture shreds of infective mucus and we were asked not to waste his time by submitting faecal specimens.

General Biggam has drawn my attention to the work of Perry and Bensted in 1929 in Cairo which certainly suggests that most cases of acute diarrhoea are due to bacilli of the dysentery group.

I shall not describe the clinical features of dysentery to you but our clinical classification of 4000 odd cases may be of some value. Cases were rapidly divided by inspection of stools into those who did not pass blood and mucus and those who did; the former—*the mildest group*—we called "acute catarrhal enteritis" (gyppy tummy) as this did not require notification and it accounted for 56 per cent.; those who passed blood and mucus were called "clinical dysentery" 20 per cent. were *mild* 22 per cent. were *moderate* and 2 per cent. were *severe*. The more experienced the person inspecting the stools the more cases he had of clinical dysentery and sigmoidoscopy of the "mildest" group showed some degree of colitis. Severity is an arbitrary thing to assess. I have seen no case of dysentery since my return who would have been sent into a hospital in Egypt whilst our mildest cases were too ill to be treated in their units. Life was threatened in all the "severe" cases. The average duration of stay in the "mildest" group was 10 days of the clinical dysenteries 20 days in two series of 600 cases including sulphaguanidine treated cases.

Treatment To control progress a graphic method of charting the frequency of stools was used with a daily description of a morning specimen. Our treatment was very simple strict rest in bed and, to conserve strength in severe cases, the use of a modified baby's napkin—a dysentery pad water only by mouth for 12 hours, then a graduated bland diet until the stools were normal morphine was given to relieve severe pain no other medicinal treatment was used except sulphaguanidine in selected cases, and we had no regrets about our early disuse of salts or castor oil. Dehydration was very rare transfusions of plasma or whole blood were used to correct it.

Dysentery was for us a clinical problem and its treatment was guided by our general impression of the patient and his stools, the presence of a tender iliac colon being a valuable indication of severity and sigmoidoscopy essential if there were frequent or abnormal stools after a week. I think the attempt to isolate the dysentery bacillus has become a fetish, quite impracticable under field conditions and giving no timely help in treatment—it is as reasonable to withhold antitoxin until the positive diphtheria swab returns, as it is to withhold sulphaguanidine and Shiga serum until the stool culture is reported on for success prompt treatment on a clinical assessment is essential.

In our large number of isolations the percentages were Flexner 70 per cent., Shiga 19 per cent., Sonne 6 per cent., Schmitz 5 per cent.

In cases of over a week's duration laboratory help is essential to exclude amoebiasis it is preferable to have the pathologist present at the sigmoidoscopy with his microscope

Probably the ideal would be for the medical officer in charge of dysentery wards to carry out his own microscopic examinations in an improvised clinical room, and this would be essential in a district where there was much amoebic dysentery I understand this was done successfully in North Africa, but it would entail the capture of a fair number of additional microscopes.

Sulphonamide Treatment

As Lt.-Col. Priest and I have already published our impression of nearly 500 cases I shall merely give a summary here.

1 *Sulphanilamide* Sixty three cases were treated and the experiment discontinued on account of poor results.

2. *Sulphapyridine* Ninety-seven cases were treated the results were nearly as good as with sulphaguanidine, but nausea, vomiting and malaise were so marked that we felt its use was only justified when sulphaguanidine was unobtainable

3 *Sulphathiazole Sulphadiazine Succinyl-sulphathiazole* Supplies were inadequate for a trial. I feel that the cheap sulphathiazole with its low

Bullen, E. & Priest W M. (1943). Bacillary dysentery Chemotherapy in its treatment. *Lancet* **2**, 69

toxicity would be ideal for field use if its action approaches that of sulphapyridine.

4 *Sulphaguanidine*

"*Gyppy tummy*" I know that many Sisters and M.O.s treated themselves and did not go sick. Seventeen patients were treated with an average stay in hospital of 6 days. Many of us remained on duty whilst on ambulant treatment for actual dysentery—it was perhaps a point of honour but the experiment justified itself it is however inapplicable to the cases with a brisk febrile onset. This was done by the Australian troops in the South West Pacific with excellent results.

Dysentery proper Three hundred and six cases were treated. The important points can be briefly summarized —

I. *Indication*

(a) *Ideally* every diarrhoeal case of sufficient severity to be admitted to hospital it is as irrational to discriminate between grades of severity as it would be in pneumonia, meningitis or gonorrhoea if saving of man-power as well as life is an object

(b) *With limited supplies* (1) All severe cases (2) Moderate cases not doing well or persisting after a week. (3) Mild cases—key personnel only

II. *Dosage* Large doses must be given, and continued until the stools have been normal for a day or two 350 grammes was our maximum, 100 grammes the average, and 30 to 40 grammes adequate in early cases. A safe system was 6 grammes at first, 3 grammes 4-hourly until the stools are two to three daily then 3 grammes thrice daily for 2 to 3 days, but this dosage was doubled in very serious cases

III. *Toxicity* Subjectively there were no toxic effects We had four cases of rubelliform rash about the 10th day and one case of sulphaguanidine kidney which recovered.

IV *Results* There is a rapid general action—the feeling of misery or malaise quickly goes and an apparent detoxication occurs we all observed this, and both PRIEST and I have experienced it. The dysenteric symptoms rapidly abate—pain goes the stools diminish in number and improve in appearance—the resolution of the inflammation was sigmoidoscopically followed in many cases

Figures are perhaps much less impressive to us than our clinical impressions—but they support the value of sulphaguanidine.

(a) Of 203 acute cases treated and these included every severe and nearly every moderate case, with some mild ones, the average stay in hospital was 17 days stools at the beginning of treatment *sixteen* on 5th day *two to three* on 7th day normal In 600 consecutive cases of all grades of severity and all methods of treatment the stay was 20 days

(b) *Control series* Thirty-six moderate cases were treated with the drug

on admission and thirteen moderate cases without it—they were as comparable as possible the control series being less severe.

(c) *Subacute and chronic cases.* If a specific bacillus could be isolated the response was good one case of 6 months standing whose apparently amoebic ulcers gave a culture of bacillus, cleared up in a week.

(d) *Death.* In the present series there were two deaths but we had two later deaths, so the final mortality rate for dysentery excluding those not passing blood or mucus was about 0·18 per cent or under two per 1,000.

TABLE II

	Stools per d on admission	Stools on 3rd day	Stools normal (days)	Stay in hospital (days)
Controls	20	4	8	18
Sulphaguanidine cases	23		6	11

One died on the 15th day but he only had 1 day's treatment; two cases reached us with pericolic abscesses one case of Shiga dysentery was treated from the 3rd day and died in spite of sulphaguanidine serum transfusions etc.

(e) *Sequelae.* Only a long follow up will show ultimate results. I know of only one who will probably have chronic ulceration, and during most of the time we could hold our cases until they were fit for duty—a few were transferred to Palestine semi-convalescent during the Alamein battle and lost sight of.

Serum Treatment

In only eight cases of Shiga dysentery was serum used since sulphaguanidine result suggested that it was unnecessary.

Flagellate Dysentery

In a few chronic cases of diarrhoea *Giardia lamblia* was found in the stool and a course of atebrin rendered the patients symptom-free.

Cholerform Diarrhoea

No true cholera was seen but an alarming minor outbreak of diarrhoea reproduced faithfully the picture of cholera, with the typical stools the patients did not seem ill enough for cholera, and all recovered rapidly.

Amoebic Dysentery

I am dissatisfied with the record of a low incidence of amoebiasis—1 per cent., we did not miss any cases of hepatic amoebiasis a the morbid anatomist

had an opportunity of confirming the diagnosis in all deaths—an empirical use of emetine in suspicious cases and an awareness of the possible meaning of unusual right basal infections saved our patients of whom we had about ten Every effort was made to diagnose amoebic dysentery the proved cases did not show the typical old chronic ulcers I have seen in England but I came to regard a curious gelatinous oedema of the mucosa as characteristic of the acute type amoebic dysentery of the proximal colon only may escape detection, as the pathologist has to depend upon bed pan specimens and has not the same chance of finding the motile amoebae as when he is working in the same room with the sigmoidoscopist.

Our standard treatment of amoebic dysentery was 10 to 12 grains of emetine, then 4 grains of stovarsol twice daily for 10 days and finally 3 grains orally of emetine bismuth iodide daily for 10 days I did not have a relapse admitted after such courses elsewhere, whilst the use of quinoxyl instead of E.B I gave us several from other hospitals—I have recently had a confirmation of such relapses from a colleague in Tripoli. Doubtless others saw our relapses and it is impossible to draw conclusions from these impressions

SHORT TERM FEVERS AND MALARIA.

Half of our medical admissions were for commonplace "English diseases one third for diarrhoea, and one-sixth for short term fevers Two thousand patients were admitted with a similar clinical picture—pyrexia often heralded by a rigor severe headache vomiting and often pain on moving the eyes there were no signs beyond frequent splenomegaly and pink-eye. We had few cases of M T malaria and no pernicious forms so that we could usually temporize and we withheld quinine unless the patient was very ill or had hyperpyrexia

The lapse of time gave us the diagnosis in some cases dysentery jaundice, one case of poliomyelitis the laboratory helped us in others—735 cases had malaria, and nineteen relapsing fever in 1153 cases the patient recovered in a few days we thought 805 of them had sandfly fever but were not too sure of this and were quite at a loss over the remaining 348

The first sandfly was discovered by Professor P A. Buxton on 6th April 1942, so we could with some support call our short term fevers sandfly fever quite similar cases occurred in the winter and patients with classical symptoms of sandfly fever were proved to have malaria I hesitate to diagnose sandfly fever with any certainty in the absence of an epidemic—one patient after a typical attack developed extensive paralysis from poliomyelitis another had his third attack of sandfly fever in another hospital and was shown to have relapsing fever

I suggest the name "short term fever" for this group it reveals one's ignorance of the cause of nearly 10 per cent of the medical admissions and further research may find several new diseases Its management is quite

simple twice daily blood films for 3 days the retention of suspicious cases for 2 weeks so that there is time for a further attack of relapsing fever to occur and the administration of quinine should splenomegaly—clinical malaria—develop. With the large numbers involved neither early blood culture nor a routine leucocyte count was possible, and full investigation had to be reserved for cases going on longer than 5 days.

Malaria

We had 735 cases (B.T 81 per cent., M.T 6 per cent. Quartan 1 per cent. clinical 11 per cent.), but I saw only one dangerously ill man—he had flown through Central Africa experience impressed us with the protean manifestations of the disease, but not with its deadliness—a dangerous impression if we had suddenly been sent to other areas. Our worst cases came from Crete during the brief early summer campaign there in 1941

The treatment was standardized quinine until afebrile then atebrin 0·1 gramme t.d.s. for 5 days, and then plasmoquine 0·01 gramme t.d.s. for 3 to 5 days the relapse rate was low but we had a good many relapses in South Africans who had not had plasmoquine.

The only death was from acute haemolytic anaemia during the plasmoquine course, perhaps a coincidence as we had two similar cases, one following sulphapyridine and one idiopathic.

THE 1 PER CENT OF TROPICAL DISEASES.

Medically fascinating but of no military importance owing to the small numbers involved yet brief mention of some of them must be made. The group is made up of pellagra thirty-one, beriberi three relapsing fever nineteen, bilharziasis eighteen, kala-azar six, leprosy one, effects of heat one.

Pellagra. Thirty-one cases

In the summer of 1941 an interesting outbreak occurred. At a nearby P.O.W. camp housing about 10,000 Libyans the occurrence of scurvy had led to a modification of diet by increasing vegetables at the expense of the meat the diet was roughly *bread* 24 oz., *meat* (raw) 1 oz *cotton seed oil* 2½ oz., *salt spices vegetables* but no milk, eggs or offal. Many cases of diarrhoea occurred in the spring, and in a fatal case Major R. PULVERTAFT raised the question of pellagra. Examination revealed over 1,000 cases of typical pellagra, of whom about 200 were moderately severe and thirty-one very severe. These latter I had in hospital, put them on a full diet with 100 mg. of nicotinic acid, and saved all but one who died from T.B. In the camp the diet was at once suitably modified by adding milk raising the meat ration to 6 oz. and issuing peanuts. The clinical features were the usual ones, but neurological and mental changes were almost absent.

Beriberi. Three cases.

A few cases occurred in the long distance desert groups, and in the

besieged Tobruk garrison. We had one fatal fulminating case of mixed beriberi and two milder cases who recovered on a mixed diet and 150 mg of vitamin B_1.

Relapsing fever Nineteen cases.

Tick-borne relapsing fever occurs in Palestine, Crete and the caves round Tobruk, as well as other parts of the Levant. It proved at first a puzzling disease—the tick bites unobtrusively and most patients were unaware that they had been bitten; spirochaetes are very scanty in the blood; the neurological complications of lymphocytic meningitis or cranial and other nerve palsies or both combined were for us unexpected; the disease was resistant to most drugs but I thought stovarsol was effective; the febrile attack was brief and similar to early malaria and sandfly fever.

Latterly we felt we could make a clinical diagnosis after a few relapses but I believe a correct diagnosis was seldom made in the first bout.

Bilharziasis Eighteen cases.

Fifteen cases were in Mauritians who came to Egypt with it; one case was in a Senussi; two only were in white troops; one infected in Durban and one at Ismailia, probably whilst watering a garden with water from the Sweet Water Canal.

It was a dull disease—terminal haematuria or cystitis as the symptoms—and the only thrill was seeing a miracidium hatch out. Its interest is its practical absence, a tribute to the troops' good water discipline.

Kala-azar Six cases.

This was of the peculiar Sudan type, with difficulty in finding leishmania, and resistance to antimony with a dramatic response to neo-stilbene. One of our cases was from an endemic zone in the Cameroons; the others were contracted in a localized area of the Sudan where large numbers occurred. The first case quite baffled us—a typhoid like illness with marked leucopaenia and splenomegaly; as soon as we were aware of the existence of the disease in the Eritrean front we watched for cases and discovered the other three. The Laboratory helped but little as the formol-gel test was only twice positive and we found leishmania only once. The cases all went to Cairo and all cleared up with neo-stilbene.

Effects of heat One case.

Although every preparation was made for cases of heat hyperpyrexia both by direct admission or as a complication of diseases under treatment, we had none. Hyperpyrexial cases occurred but were all due to infections. We were in a region of low humidity although shade temperatures commonly exceeded 105° and once reached 120° F.

It is probable that this war will lessen the popularity of the topee—in the Middle East merely a clumsy headgear that finally became optional. The

experimental work done by MARSH in Persia on rabbits and presented to this Society should have rung its death knell a decade ago.

One fatal case of heat exhaustion occurred—a soldier who had had an attack in the Red Sea arrived in Egypt during a heat wave he was admitted with a week's history of anorexia, weakness and loss of weight, had a blood pressure of 62 mm. of mercury with a blood count of 6½ million red cells, and 130 per cent haemoglobin he developed anuria and died of some type of renal failure the blood urea being 320 mg per cent. He failed to respond to fluids by all routes. The autopsy gave no further clues.

CONCLUSION

Let me crave your indulgence for a very free expression of opinion by a tropical tyro on your special subject. I should speak of these matters with less assurance had I twenty instead of two years experience

DISCUSSION

The Chairman (Sir Harold Scott) Gentlemen, as regards Colonel BULAER's paper I have nothing to say at present in fact, the less I say the better—so many people would like to speak who are more *au fait* with the subject. The ratio of three medical cases to two surgical in war time is unusual if not unique. When one thinks of previous wars before the last the proportion was twenty or more medical to one surgical. Again, the characters of diseases seem to alter from time to time. In the South African war I had a large number of cases of dysentery under my care, and I found that the *concentrated* sulphate gave wonderful results instead of negligible, as Colonel BULAER found in the present campaign. Patients used to react in 24 to 48 hours and stools would be reduced in number to three or four in that time Such treatment was found to succeed in the bacillary form only not in the amoebic. We used to give it in doses of 10 grains in a drachm every hour till the stools became faeculent.

Lt.-Col C H Barber I would like to ask Colonel BULAER the result of treatment by dysentery serum? He only used it in eight cases, with good results in one Was the good result due to sulphaguanidine? In the other seven cases it would be interesting to know the effect of the serum. I was glad to hear Colonel BULAER's comments on the topee and heat-stroke. I think the effects of heat are most often due to the body getting overheated not from the rays of the sun but largely from radiation from the ground. You do not get it in the hill stations where the sun is still stronger I have long advocated a topee or hat made of light straw which does not heat the head and yet protects from the sun's rays. There were experiments years ago on the effect of the direct rays on monkeys' heads—before the experiments on rabbits—and it was shown that you could expose a monkey's head for hours to sun without harm provided you kept the body cool Talking about pellagra it was not clear whether

protein was added as well as nicotinic acid, or whether the amount of protein was reduced

Sir Phillip Manson-Bahr congratulated Colonel BULMER on his excellent and essentially clinical paper As one who during the last war had on many occasions been overwhelmed by avalanches of bedpans he could sympathize with the question of prompt diagnosis of bacillary dysentery When he compared the record of sixty cases of dysentery a week with as many as ten times that number during the Gallipoli epidemic in 1915 and in Sinai in 1917 it showed what a remarkable change had occurred in the incidence of bacillary dysentery It was at that time quite impossible with the limited laboratory facilities at our disposal to attempt anything in the way of large-scale isolation of specific dysentery bacilli and therefore it is possible to agree that the introduction of sulphaguanidine treatment has rendered these bacteriological refinements from the practical viewpoint unnecessary The mere statement that under this treatment the average case was passing normal stools within five days was ample demonstration if further proof were needed of the efficacy of sulphaguanidine treatment.

Recently there had been some closely argued criticism that the claims of bacteriophage treatment elaborated in Alexandria had been neglected. Extravagant claims had been put forward and he had met many who stated that its effects in "gyppy tummy and other explosive diarrhoeas had been widely recognized and that this treatment had much support in the Navy He, himself had remained unconvinced, as he was unaware of any carefully controlled series of cases subjected to bacteriophage treatment, and he would be glad if this bogey could be laid to rest.

As regards the outbreak of pellagra in Italian prisoners, he could not fail to be struck by the way in which that history under similar circumstances in 1916 had repeated itself But what a change had been effected in treatment of this disease by nicotinic acid! Most assuredly in those far-off days the great majority of these acute cases would have succumbed.

As regards the great group of pyrexias of uncertain origin he would like to enquire whether sternal puncture, on which several papers had recently appeared, was found to be of real value in diagnosing obscure or evanescent infections with *Plasmodium falciparum* It would appear that this might be a valuable method, for 25 years ago there was, as now a tendency to lump all febriculae together under the convenient camouflage of sandfly fever Subsequently many of these cases relapsed and were found to be in reality subtertian malaria.

Professor P A Buxton In the beginning of his paper Colonel BULMER gave an account of that enormous camp in the desert roughly between Suez and Cairo There was one point about it, which interested me very much when I lived in it in 1942, a point to which he did not refer In that large group of

base hospitals there were a considerable number of able relatively young clinicians who had had no previous experience of the tropics but had a real knowledge of modern clinical methods and medicine It was interesting and encouraging to see how they were mopping up the special tropical subject. I hoped at the time that one of them would bring something fresh to the Society of Tropical Medicine and that hope has been fulfilled today

Dr C C Chesterman asked whether cases of pellagra had been cured with nicotinic acid alone or whether riboflavine had also been used. He also enquired whether in Field practice agglutination tests for enteric fevers were still being used.

Air-Commodore T C Morton I would like to ask Colonel BULMER two questions. The first is in connection with desert sores I wonder if he found a certain percentage were infected with K.L.B We found that a convoy of troops from Palestine had a high incidence of diphtheria carriers and were suffering from desert sores. In two instances we isolated virulent K L.B. from these sores on tellurite media. One of these cases subsequently developed a typical post-diphtheritic paralysis. These desert sores, which were secondarily infected with K.L.B rapidly healed after receiving anti-diphtheritic serum. Captain CRAIG R.A.M C., described a similar condition in the last war The second question is about the fatal case of heat exhaustion he described the symptomatology is identical with the type of case we used to get in Northern Iraq and Persia, and I would like to know if the case was treated with intravenous normal or hypertonic saline.

Dr H S Stannus Of the many questions which Colonel BULMER has discussed, the two that seem to be of greatest importance are the two failures which he has mentioned—the failure to entirely prevent dysentery in a stationary camp and the failure to prevent pellagra in a Libyan internment camp. One would like to ask him in regard to dysentery which he still holds is carried by the fly whether he can give us any other more detailed information upon the point? Is it due to food contamination and, if so, when, where and how? The prevention of dysentery is the important point. Secondly as regards pellagra, it is an extraordinary thing that with our present-day knowledge we cannot yet devise diets which will prevent deficiency diseases.

Brigadier George Macdonald I should like to thank Colonel BULMER for his paper and to comment on two points. First, I should like to agree with his suggestion that training should be divided into a first part in the United Kingdom and a second part abroad. I think this division most important as the essential basic training best given in the United Kingdom, cannot contain sufficient detail to apply to all the many theatres of war to which people might be sent. Therefore at home training should be restricted to basic principles,

and abroad it should be pushed ahead with emphasis on the detail of locally important diseases and their control.

The second point is the one raised by Colonel BULMER, and again by the last speaker the failure to control dysentery in the Middle East. I would ask that Fellows of the Society reserve any opinion until figures can be produced. I have just returned from the Middle East and, though I have not come prepared with figures to illustrate the incidence I know their general character The incidence of dysentery is very much lower than it has been in previous campaigns in that part of the world, and the total admissions to hospital for all medical causes, including tropical diseases were I think, less in 1942 than in any theatre of war temperate or tropical, in the 1914–1918 war We should, therefore, ask that figures giving the annual incidence per 1 000 troops should be produced before we agree that there has been a failure to control dysentery in the Middle East.

Dr A Felix asked Colonel BULMER about his experience of typhoid fever Typhoid fever had not been mentioned today presumably because it was not recognized as a tropical disease, but in a paper which Colonel BULMER published earlier this year* he had commented on the severity of the cases and the high mortality rate in patients who had been inoculated with T.A.B vaccine. The paper also contained the statement that the disease remains uninfluenced by any treatment but good nursing Dr FELIX asked if Colonel BULMER, in making this statement, had considered treatment with anti typhoid Vi + O serum

Professor P A Buxton On the matter of diarrhoea and dysentery I have had a limited experience which I would like to record. I was never up the line in Egypt where there were areas where sanitation was imperfect and flies were common I lived from the end of March to the end of June, 1942 in an area of base hospitals and large standing camps During that time which should have been the fly season house flies were rare even in kitchens and messes. In this matter I find myself differing from Colonel BULMER, for I do not believe that dysentery and diarrhoea contracted on the spot were fly-carried As an entomologist, my tendency would be to incriminate the fly but in that area I could not. On a second point I have difficulty in accepting the view he subscribes to that much of the 'gyppy tummy is bacillary dysentery I believe that the search for the bacillus was made often, and consistently the organism was not found on many occasions. I have no theory to offer as to what did produce local dysenteries and diarrhoeas

Colonel J S K Boyd Colonel BULMER said that the relative proportions of cases admitted to hospital were three medical to two surgical. I think

* BULMER E (1943) *Brit med J* 1 374

this must be taken as local as it is not the proportion of medical cases to battle casualties throughout Middle East.

As regards the early bacteriological diagnosis of dysentery I agree that the necessity for this has been changed by the introduction of the sulpha drugs. We have now given up the routine bacteriological examination of dysentery stools, but I do not regret that we adopted it for the first few years. It has given us a clear idea of the incidence of the different types of dysentery and has proved excellent training for pathologists who had no previous experience in that type of investigation. I might have brought with me an analysis of some 60,000 cases of dysentery. It will interest you to know that the percentage of amoebic dysentery was less than 5, and that, of the different types of dysentery bacilli isolated, Shiga's bacillus comprised approximately 20 per cent.

As to serum treatment, I think Colonel BULLMER's ideas would have been different if he had been in Middle East in the pre sulphaguanidine days. At that time I saw with Colonel HAMILTON FAIRLEY a number of very severe cases of bacillary dysentery. Such cases have been rare in later years, and I attribute this largely if not wholly to early treatment with sulphaguanidine. For Shiga infection we used a concentrated antitoxin in doses of 100,000 units. This produced an immediate amelioration of symptoms lasting about 24 hours, but thereafter the patient's condition again deteriorated. We formed the opinion that if serum was given at an early stage it had a more permanent effect because it allowed the patient's natural processes of defence to come into action, but in later stages the effect was temporary only. We came to the conclusion that the best treatment for acute toxic cases was a combination of sulphaguanidine and antitoxin. Nevertheless, what Colonel BULLMER says is correct, and nowadays in sulphaguanidine-treated cases there is very little need to use serum.

We have been increasing greatly the use of sigmoidoscopy and have found some unusual pictures. I think some existing conceptions may need revision in the light of this experience. Colonel BULLMER referred to one such case.

Sir PHILIP MANSON BAHR has raised the question of bacteriophage therapy. If I may I shall say a few words about this, as we have carried out some investigations subsequent to Colonel BULLMER's departure. In the advance to Tunisia we captured large quantities of German medical stores, including an excellent polyvalent bacteriophage which was the standard treatment for bacillary dysentery in the German army. We divided a prisoner-of-war camp into two sections, *and treated all cases of bacillary dysentery in one section* with standard bacteriophage treatment, and those in the other half with ordinary saline treatment. Bacteriophage treatment was started the moment a patient complained of any intestinal symptom. Admission rates for dysentery were practically identical in both sections, and the duration and severity of the disease were not dramatically different. If anything, the figures in the bacteriophage

series were slightly better but the difference was not statistically significant. We also carried out an experiment in prophylaxis along the lines recommended by a German observer All the inmates of one cage were given bacteriophage on three successive days Contrary to what has been claimed elsewhere, the subsequent incidence of bacillary dysentery in those so treated did not differ from that in untreated cages There was no evidence of prophylactic action

In addition we had an unexpected confirmation of our findings In a certain area there is an internee camp in which considerable numbers of enemy aliens (chiefly Italians) are confined. These enjoy certain amenities including the privilege of being visited by relatives, who come periodically bringing presents including large quantities of bacteriophage which is taken prophylactically and as treatment. Nearby is an Italian prisoner-of-war camp in which no bacteriophage is used. The sanitation of the two camps is identical in both cases under our military control We were able to get figures of the admissions for dysentery in the two camps over a period of months and found that the prisoner-of-war camp was rather better than the other

Colonel BULMER said he had a case of malaria with haemolysis due to plasmoquine I would like to know how he decided it was plasmoquine poisoning and not blackwater fever

Colonel BULMER mentioned some 1 100 cases to which he was compelled for want of a better to apply the diagnosis of sandfly fever I think this diagnosis is run to death It is probable that the majority of these cases were not sandfly fever and I think it would be much better if we used an honest diagnosis such as pyrexia of unknown origin stating the number of days of fever *e.g* P U O 3 day P U O 5 day etc. This might lead to the differentiation of types which are at present camouflaged under the blanket diagnosis of sandfly fever

As regards pellagra and diet, apart from the actual scale of rations provided there is another factor to be considered. Some of these native races refuse to eat certain components of the diet provided for them. A diet may be in every way adequate, yet for the above reason fail to prevent deficiency disease.

The President I would like to interpolate a word with regard to what one contributor said about desert sore I can trace it a good deal further back than he has done When I was in the R.A.M C in the South African war I saw a good deal of veldt sore We got no results from ordinary treatment of ulcers until I examined them and found the diphtheria bacillus in the discharge I was then able to get antitoxin and applied swabs soaked in antitoxin to the sores and they cleared up wonderfully One case had definite post diphtheritic paralysis That was in 1901

Lt -Col Bulmer (in reply) hoped that he had not given rise to misconceptions by compressing the subject unduly He thanked Colonel BOYD for dealing with bacteriophage in the treatment of bacillary dysentery

Many speakers had spoken of the value of Shiga anti serum he thought the introduction of sulphaguanidine had made its use seldom necessary but he had no experience of the results of serum treatment alone. The orders from the Medical Directorate in the Middle East were that serum must be used on all serious cases of Shiga dysentery the speaker had accepted the responsibility of withholding serum in such cases, and using only sulphaguanidine, the response had been as satisfactory as when both were used. The chart shown on the screen which provoked the discussion was intended to demonstrate a simple method of recording progress, and not the value of specific treatment which could not be judged from a few striking charts.

The treatment of the pellagra cases was by giving them a full, balanced diet to the seriously ill ones nicotinic acid was administered, but riboflavine was not available.

Sir PHILIP MANSON BAIR's questions about bacteriophage had been answered by Colonel BOYD Colonel BULMER did not think that missed cases of malaria accounted for many of the unsatisfactory group of short term fevers, although sternal puncture was not carried out it was certain that cases of relapsing fever were missed.

The speaker did not agree with Professor P A. BURTON's suggestion that "gyppy tummy was not dysenteric, and unsuccessful attempts to isolate the dysentery bacilli were due probably to the absence of selective media.

Air Commodore MORTON's question about the diphtheritic desert sore was of great importance—in the speaker's cases a few showed diphtheria bacilli one unexpected fatality occurred In Palestine the Australians the speaker believed, studied this subject very fully and they did not get positive swabs from the sores until an outbreak of faucial diphtheria occurred in that country It is probably true to say that desert sores are due to unknown factors, and are not diphtheritic like any other abrasion or wound, they can be infected secondarily by the Klebs Löffler bacillus, and a type of wound diphtheria be produced, but in Egypt the number of such cases was negligible

The patient with heat exhaustion did not have cramps, and he was given salt in large doses, both by mouth and intravenously

Dr STANNUS's question about where flies, if they are dysentery carriers, can infect food, is difficult to answer the speaker thought bread was possibly contaminated, as there are ample opportunities between the field bakeries and the unit kitchens

In reply to Dr FELIX, the speaker said that specific anti-sera were not used in the treatment of typhoid fever

Colonel BOYD had raised many interesting points, and corrected several of the speaker's impressions. Colonel BOYD had access to the official Middle East statistics, Colonel BULMER had merely his own hospital's records. The fatal case of haemolysis attributed to plasmoquine might have been blackwater fever but could not be dogmatically ascribed to malaria, as parasites could never be discovered.

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COMMUNICATIONS

BACTERIOPHAGE THERAPY IN BACILLARY DYSENTERY

BY

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The discovery of bacteriophage by TWORT in 1915 and D HERELLE in 1917 opened up the possibility of using this agent therapeutically in the treatment of certain bacterial diseases, of which bacillary dysentery on account of the superficial and accessible situation of the lesions in the bowel, appeared to be *par excellence* one in which it was likely to be successful. Many observers, including D HERELLE himself claim to have obtained striking results from its use in this disease, but others have found it to be without effect. All trials hitherto made in military practice fall into the latter category and for this and other reasons it has never been adopted as a standard form of treatment in the Army

Recently a unique opportunity arose to make a thorough investigation of this subject the results of which are presented in this paper

LITERATURE ON BACTERIOPHAGE THERAPY IN BACILLARY DYSENTERY

Difficulty has been experienced in gaining access to all references on this subject owing to active service conditions It is believed that the majority of important papers in English have been consulted but many in other languages have not been obtainable In certain cases it has been necessary to rely on excerpts from *Bulletins* and where the original has not been consulted a note to this effect is made

DAVISON (1922) (original not available) had a 58 per cent mortality in twelve bacteriophage-treated cases of bacillary dysentery in children Flexner's bacillus was isolated in ten of the cases and of eight strains tested seven were susceptible to bacteriophage Large and frequent doses were used—from 5 c c to 1 300 c.c being given Seven cases were treated orally five by enema. Failure was attributed to the fact that therapy was commenced too late in the course of the disease

COSTA CRUZ (1924) in a paper which gives no statistics and no figures as to number of cases concluded that Bacteriophage is easily the best treatment for bacillary dysentery Its action surpasses all other agents—the symptoms diminish considerably in 4 to 8 hours and the illness enters into its convalescent stage in 24 to 48 hours after administration.

SPENCE and MCKINLEY (1924) (original not available) treated twenty cases of Shiga and Flexner infection nineteen within the first week of the illness with 10 c.c. of bacteriophage t.d.s. orally. The mortality rate was 10 per cent. and the average stay in hospital 5·8 days (a somewhat striking contrast). A control group in another hospital (? number) not treated by bacteriophage had a mortality rate of 40 per cent. and an average stay in hospital of 12·6 days.

CHOUDHURY and MORRISON (1929) (original not available) treated eighty cases of Shiga and Flexner dysentery with a polyvalent bacteriophage giving 2 c.c. t.d.s. the 1st day and b.d.s. thereafter. The mortality rate was 4 per cent. No reference to controls is available.

TAYLOR, GREVAL and THANT (1930) (original not seen) treated cases in which only a short interval had elapsed between onset of the disease and treatment. 2 c.c. of polyvalent bacteriophage was given three times daily. In fourteen cases of Shiga infection there was a mortality of 14 per cent. as compared to 17 per cent. in a control group. In six *treated Flexner cases and a control group there was one death in each series.*

COMPTON (1929) published a "record of sixty-six cases with inferences." He classified his results as very good thirty-five, good ten, moderately good six, partial failure five, failure ten, but of the failures four were advanced cases before treatment was started and did not have a fair chance. No controls were maintained. The bacteriophages used in this experiment were good ones and had been tested *in vitro*. "During the treatment a noteworthy lowering in the death-rates from dysentery was observed. Distribution of bacteriophage to patients in a region means an increased proportion of bacteriophage carriers among the population with in all probability a correspondingly increased distribution of bacteriophage in the food and drink."

RIDINO (1930) observed, over a 2 year period, sixty cases of bacillary dysentery of which records were maintained in forty-eight. Thirty-five were treated with bacteriophage, thirteen were kept as controls. Each case was thoroughly investigated, clinically and bacteriologically. RIDINO concludes (*a*) it is probable that bacteriophage ingested by mouth is quickly eliminated or destroyed by the human body, (*b*) the contents of the intestines in dysentery do not appear to be a suitable medium for the process of bacteriophagy, and (*c*) the clinical course of acute bacillary dysentery is not altered by the oral administration of bacteriophage. RIDINO's clinical findings are open to the criticism that most of the patients had been ill for some days before treatment was started.

QUINTANGAL DES ESSARTS (1933) treated 180 cases of bacillary dysentery occurring in 29 days on board two ships at Brest. Fifty-nine were identified, sixteen Shiga, thirty-eight Flexner and five paradysenteries. 165 were treated with polyvalent Shiga Flexner bacteriophage prepared from convalescent stools, which was active and proved innocuous. 5 c.c. was given in alkaline water the 1st day, 10 c.c. the 2nd and 3rd days, and 5 c.c. the 4th day. The "results were remarkable. After the 2nd or 3rd day blood and mucus disappeared, and after 4 days the stool appeared normal microscopically. None of the cases had severe tenesmus. There were no controls. The author also claims to have arrested an outbreak among infants in a holiday camp by giving bacteriophage prophylactically. Again there were no controls.

KRASIL and ROSA (1933) (original not seen) reported sixty-eight cases of which half were maintained as controls; 90 per cent. of the Flexner strains were found to be susceptible to bacteriophage. The dose given was 3 c.c. to 5 c.c. orally every 12 hours. There were three deaths in the control group and four in the treated group. The period of hospitalisation was slightly but not significantly lower in the treated group.

JOHANNOW, ENNS and KAASE (1933) (original not seen) found that bacteriophage did not affect the clinical course of dysentery. Seventy infants under 2 years of age were treated with 1 ounce of bacteriophage hourly. Only seventeen out of ninety four strains tested *in vitro* were susceptible to the bacteriophage employed.

MCCAY (1934) describes the treatment of bacillary dysentery in Calcutta with bacteriophage prepared in Shillong. Anti-dysenteric serum was used in a large proportion of cases. No statistics are given. The author states "I hope that bacteriophage enthusiasts will duly publish a series of such cases with controls. If bacteriophage has no other

claim to success at any rate it cannot be said that it makes the patient's diarrhoea worse than it was or in any way stimulates the intestinal tract.

VAILL and MORTON (1937) treated 200 cases of dysentery with bacteriophage in New Jersey but kept records of only twenty two cases Figures are given for these which convey little information as only one case is cited as a control The authors prefer a strain-specific bacteriophage which has been adapted to the patient's strain of bacillus by serial passage At the same time they emphasize the importance of instituting bacteriophage therapy as soon as possible after the onset of the disease They do not explain how these two paradoxical requirements are to be reconciled.

MURRAY (1938) treated 146 cases of bacillary dysentery with bacteriophage between 1931 and 1937 Usually the treatment took 2 weeks seldom longer than 3 weeks There were no controls no mention is made of the isolation of organisms nor are details of the bacteriophage given. The author concludes (1) that bacteriophage is by far the best method of treating bacillary dysentery (2) that failure in treatment can be attributed to the fact that a reliable bacteriophage has not been used and (3) that to prove its value a controlled series is required.

HALER (1938) treated an epidemic of dysentery in a home for children—thirty two children staff of seventeen. There were seven cases of Sonne infection but the writer also refers to an atypical organism which he believes to have been evolved from the Sonne bacillus by the action of the bacteriophage This mutation was not substantiated experimentally Everyone was given bacteriophage (dose not stated) thrice daily for a fortnight and one dose daily afterwards The epidemic ceased 2 days after giving bacteriophage and there have been no cases for a year There were no controls and the author states that this cessation of the epidemic may have been a coincidence.

GUTHOF O (1941) (original not seen) a battalion M O in a German infantry regiment, treated bacillary dysentery with Dysentery Polyfagen (Behring) fifty-two adults were treated with good results in 2 to 4 days and in three children with severe infections the results are also stated to have been satisfactory No controls are mentioned in the review consulted.

WHEELER and BURODORF (1941) investigated, as a possible means of establishing a diagnosis, the presence of bacteriophage in the stools of patients who had suffered from bacillary dysentery They were successful in isolating bacteriophage from 3 to 9 weeks after the date of the attack in a number of cases Several individuals (fifteen according to their tables) gave concurrently positive culture and bacteriophage tests for varying periods of time up to 2 weeks Organisms isolated from these individuals were susceptible to the bacteriophage strain but apparently the in vivo action was not sufficiently strong to eliminate the organisms

KLIEWE, H and HELMREICH, W (1941) (original not seen) stress the importance of ensuring that the bacteriophage used is potent against the local strains In *Poland* many of the local strains of dysentery bacilli were not susceptible to German bacteriophages A test of the prophylactic value of locally prepared bacteriophage mixtures was made by giving 113 soldiers while in a fasting state a dose of sodium bicarbonate followed by 10 c.c. of the mixture in half a cup of tea or coffee on three successive mornings 230 men of the same unit were left untreated to serve as controls In the course of the following 8 weeks no cases of dysentery developed among the 113 bacteriophage-treated men while ten cases occurred among the controls The therapeutic value was also tested It was said to prove particularly effective in cases of mild or moderately severe Flexner Y dysentery In cases of severe illness there was frequently an exacerbation and only occasionally improvement sixteen carriers were cured after they had received bacteriophage therapy on 3 successive days

SOERMAN (1941) (original not seen) reports on fifty cases of bacillary dysentery—seventeen adults and thirty three children treated with polyphage All recovered and in most cases the severe symptoms disappeared after oral administration of the bacteriophage In our opinion the polyphage is a valuable asset in our armament against the acute bacillary dysentery intestinal infections " No reference is made to controls.

COMPTON (1942) cites case mortality rates in Alexandria Cairo and the rest of Egypt, and suggests that the falling mortality rate of dysentery in Alexandria is to be attributed

to the use of bacteriophage The argument is wholly inferential and is based on figures which do not substantiate claims made elsewhere by this author to wit, that the early use of bacteriophage prevents the development of dysentery If the latter argument is correct and if as the author says it has become the established rule to treat acute bacillary dysentery and its frequent precursor acute enteritis " with bacteriophage why is it that the total annual number of cases of dysentery has averaged about 650 during the period (1928–40) and has not gone down to any great extent "

HEGLER (1943) describes the treatment of dysentery with bacteriophage without giving much detail and finishes It is not possible to give a conclusive decision on the value of bacteriophage " (Among the German medical officers HEGLER is regarded as the leading authority on dysentery and its problems)

Perusal of these references reveals much diversity in result and opinion. It is noteworthy that in the majority of trials no controls have been maintained, and that practically all observers who have instituted this check report guardedly or unfavourably on the results obtained.

PREVIOUS ARMY TRIALS OF BACTERIOPHAGE THERAPY

Prior to the present experiment, four small-scale trials of bacteriophage therapy were made in the Army in Middle East, none of which have been published. Two of these were made before the establishment of Middle East Command and neither gave results of any promise. The third was carried out by Surgeon-Commander D C WILSON R.N., and Major J E. JAMESON R.A M C Here again the results were unconvincing Correspondence on this trial has appeared in the columns of the *British Medical Journal* (1942, 18th July p 81 and 5th December p 676) The fourth was a carefully-controlled trial made by Capt. R P HENDRY R.A.M C Thirty two cases were treated, of which eighteen were in the control series, and fourteen were treated by bacteriophage Capt. HENDRY in his report drew the following conclusions

The general impression gathered from observing the progress of the thirty two patients in the ward and subsequently from studying the above tables, was that the bacteriophage group made slightly better progress than the control group. But the difference was so small that had an additional dozen cases been treated the result might easily have been reversed.

Against these and other negative findings the supporters of bacteriophage treatment advance two arguments one that the bacteriophage used has not been potent against local strains of dysentery bacilli the other that the treatment has been started too late in the disease If substantiated, both these objections are valid As to the first, the bacteriophage used in these Army experiments was a preparation in wide use in Alexandria and Cairo in civil practice, regarding which enthusiastic claims are made by local practitioners. As to the second, while certain of the cases were some days old before bacteriophage therapy was started, others were in the early stages, in which good results are said to follow almost invariably the latter did not respond to treatment any more quickly than the former

An Unprompted Experiment

Unknown to the writers of this paper an entirely unprompted and unsupervized experiment in bacteriophage therapy has been in progress in the same area in Middle East in which the investigations to be recorded later in this communication were carried out, and it has been possible to obtain accurate data which are of considerable interest

The test population is provided by the inmates of an internee camp where male enemy aliens mainly of Italian nationality are detained. This camp is run under British military supervision on much the same lines as a prisoner-of war camp but has greater amenities Among other privileges the internees are allowed to receive visitors and at stated intervals wives and other relatives arrive bringing with them gifts which have to be declared. The favoured gifts are flowers, fruit, sweets books and in the same category of importance (mute witness to the local faith) bacteriophage It is improbable that its use is universal but it is a fact that large quantities of bacteriophage are imported and taken both prophylactically and as treatment.

A few miles away in identical surroundings and under the same sanitary supervision, is an Italian prisoner-of-war camp where bacteriophage is unknown

Accurate records are maintained of cases of clinical bacillary dysentery with typical blood and mucus admitted to hospital from both camps, in each of which the numbers at risk run into thousands The rate of admissions per 1 000 in a period of four months is shown in Table I

Table I

Rate per 1 000 of admissions to hospital for clinical dysentery

	Internee Camp ('Phage used.)	P O W Camp (No phage)
May	3 3*	3 19
June	8 23	2 4*
July	4 88	1·60
August	3 32	1 42

The bacteriophage in question is of course one or other of the local products which are for sale in most chemist shops in these parts The beneficial results of its use are not apparent in these figures.

Scheme of the Present Investigation

Bacteriophage was according to the statements of German medical officers, the standard treatment for bacillary dysentery in the forward troops of the German Army in Africa. The preparation used is Ruhr Bakteriophagen Polyvalent Behringwerke, and carries the Bayer trade mark. It is elegantly put up in special brown glass bottles with rubber stoppers and viscap in

volumes varying from 50 c.c. to 500 c.c. Large quantities of this bacteriophage were captured during the Axis retreat from El Alamein.

It was decided to use Ruhr Bakteriophagen in the treatment of cases of bacillary dysentery occurring among certain German prisoners of war but to restrict it to one half of the community and to place the other half on standard non bacteriophage treatment, thus obtaining comparative figures from which the value of bacteriophage treatment might be assessed

Camps in which prisoners of war are incarcerated are divided up into sections or cages which are more or less identical These are equipped to take the same number of men in well-spaced tents, they have the same amenities, the same cooking arrangements and food and the same sanitary arrangements. The population is relatively stable, and the inmates of the various cages do not mix to any extent The standard of health and freedom from epidemic diseases compares favourably with that of any other community in Middle East.

The medical arrangements are alike in all cages. Each has its medical officer (a German prisoner of war) and Medical Inspection Room. Trivial cases of all kinds are treated in quarters. Patients who are sufficiently ill to require special attention are removed from the cage and admitted to a very well equipped camp hospital, from which, if the condition is serious or if the patient is likely to be ill for some time they are transferred to a large prisoner of war hospital which forms a section of a British General Hospital. This prisoner-of war hospital is staffed by German medical officers, but is administered by the staff of the British General Hospital and supervised by its specialists. Dysentery cases with blood and mucus are first admitted to the camp hospital but are invariably passed on to the other as soon as possible.

In the prisoner-of war camp selected for the trial two separate but strictly comparable communities were created by a random grouping of cages into two series. Dysentery cases from one series received bacteriophage treatment those from the other did not. A further cage was set aside for a small experiment in prophylaxis.

Throughout the trial the patients were under the charge of their usual medical officers and, except for the special instructions given in respect of the bacteriophage therapy no change was made in the normal routine of medical treatment employed by the German medical officers. In the main hospital all cases were attended by one officer who remained unchanged throughout the trial

The bacteriological examination of specimens from patients was carried out in a Mobile Bacteriological Laboratory under the charge of one of the authors (B P), who also held a watching brief over the progress of the cases and the maintenance of statistical records The typing of the Flexner strains, the titration of the bacteriophages, and other similar tests were carried out in the Central Pathology Laboratory

The main experiment was continued over a period of two months, from

10th May to 9th July Although this is a season in which cases of bacillary dysentery are usually common, the incidence on this particular occasion was low Nevertheless the numbers which occurred are sufficient to be significant.

Objects of the Investigation

The objects of the investigation were —

(1) To determine if bacteriophage has any prophylactic action This was carried out as a small independent experiment

(2) To determine if the administration of bacteriophage in the early stages of bacillary dysentery will abort the disease, *i.e* reduce the number of cases which require admission to hospital.

(3) To determine if bacteriophage therapy will modify the course of the disease and reduce the length of time which the patient remains in hospital

(4) To study by laboratory methods certain aspects of bacteriophage therapy

Preliminary Considerations

(*a*) *Potency of Ruhr Bakteriophagen*

Tests of the potency of Ruhr-Bakteriophagen were made by the patch technique elaborated by Craigie and Yen (1938) for the investigation of Vi strains of *Bact typhosum* Ten times dilutions of bacteriophage were used without intermediate dilutions as accurate end points were not considered essential. The figures recorded are the highest dilution producing a clear window of lysis in a patch of culture

(i) The potency of Ruhr-Bakteriophagen was tested against stock cultures of dysentery bacilli typhoid paratyphoid bacilli and a recently isolated strain of *B coli* Parallel titrations were made with a French bacteriophage sponsored by D Herelle, and with an Alexandrian bacteriophage The results are shown in Table II

It will be seen that Ruhr Bakteriophagen is of high potency and wide polyvalency In both these respects it is superior to the French and the Alexandrian preparations.

(ii) The potency of Ruhr-Bakteriophagen was tested against all strains isolated in the course of the investigation with the exception of two which were accidentally lost For convenience only a 1/1000 dilution of the bacteriophage was used The results are recorded in Table III. All strains tested were found to be susceptible the majority highly susceptible, to the action of this bacteriophage.

(*b*) *Powers of Resistance of Ruhr Bakteriophagen*

To determine if bacteriophage remained potent and was unaffected by its passage through the stomach and bowel the faeces of a number of patients under treatment with this preparation were examined.

TABLE II

TITRATION OF VARIOUS BACTERIOPHAGES AGAINST TYPE STRAINS OF DYSENTERY BACILLI TYPHOID-PARATYPHOID BACILLI AND *B. coli*

	Sh.	Sch	Shm	Flex. I	Flex II	Flex III	Flex IV	Flex V	Flex VI	Boyd I	Boyd II	Boyd III	*Bact T ph*	*Bact para A*	*Bact para B*	*Bact coli*
Ruhr Bakteriophagen, polyvalent Behringwerk Bayer	1 000	100	1 000	1,000	1 000	100	10	1 000	1 000	1 000	10	10	10	—	—	10
Bact.-dysenteri-phage Laboratoire du Bactériophage (Paris) under the scientific control of Professor d'Herelle	10	10	10	100	100	1 000	10	100	10	10	—	—	—	—	10	<10
Anti-diarrhoea polyphage. Bacteriophage Research Institute of Egypt (Bacillary dysentery diarrhoea, cholera)	100	10	100	10	10	10	—	100	< 10	<10	10	<10	<10	<10	<10	<10

NOTE.—1. The figures indicate the dilution of bacteriophage which, using CRAIGIE's technique, gives a clear window of bacteriolysis—in a patch of culture. The end points between 10^{-4} 10^{-5} 10^{-6} and 10^{-7} are not worked out. <10 indicates that bacteriophage action was present but insufficient to give a clear window in a 1/10 dilution.

2. The only specimen of "Anti-diarrhoea polyphage" available was beyond the alleged expiry date when tested. As, however, it had been kept at refrigerator temperature from a date which long preceded its expiry it is probable that no material deterioration had occurred.

TABLE III

ACTION OF HUIR BACTERIOPHAGEN DILUTED 1/1 000 ON STRAINS ISOLATED IN THE COURSE OF THE INVESTIGATION

	Isolations from Test Series.					Isolations from Control Series.					Total				
	C	C—	SCP	P	Nil	C	C—	SCP	P	Nil	C	C—	SCP	P	Nil
B. dysenteriæ Shiga	13	—	—	1	—	13	5	—	1	—	26	5	—	2	—
para-Shiga (?)	1	—	—	—	—	—	—	—	—	—	1	—	—	—	—
Schmitz	1	—	—	4	2	4	—	—	—	—	8	—	—	4	2
" Sonne	—	—	—	—	—	4	—	—	—	—	4	—	—	—	—
" Flex. I	20	2	*	1	—	11	3	3	—	—	31	4	4	1	—
" II	4	1	3	—	—	6	1	—	—	—	10	2	3	—	—
" III	—	—	—	—	—	—	1	—	—	—	—	1	—	—	1
" IV	—	—	—	—	—	—	—	—	—	1	—	—	—	—	1
" V	7	1	*	—	—	9	—	1	—	—	10	1	3	—	—
" (unclass.)	1	1	—	1	—	1	—	—	—	—	2	1	—	1	—
Total	50	5	6	7	—	50	9	3	1	1	100	14	9	8	3

Note.—C = complete lysis. C— = almost complete a few tags left. SCI = semi confluent plaques. P = plaques.
Of the strains shown in the Nil columns two cultures of *B. dysenteriæ* Schmitz were accidentally discarded before being tested against more concentrated bacteriophage. The strain of *B. dysenteriæ* Flex. IV was susceptible to a 1 in 10 dilution.

TABLE IV

PROPHYLACTIC ACTION OF BACTERIOPHAGE

	Control Cages. (No Bacteriophage)				Cage on 3 Days Prophylactic Bacteriophage			
	Average Strength	Dysentery Admissions.	Rate per 1 000	Rate per 1 000 over 1 Weeks.	Average Strength	Dysentery Admissions.	Rate per 1 000	Rate per 1 000 over 1 Weeks.
—1 week	2113	7	3 31	11 37	672	2	2 98	37 59
—2 "	2081	10	1 8		678	4	5 90	
—3 "	2105	5	2 37		701	6	8 56	
—4 "	2107	2	0 92		707	7	0 0	
3 days prophylactic bacteriophage					—	Nil	—	—
1 week	2193	7	3 19	10 49	705	3	1 25	10 5
2 "	2204	3	1 36		751	1	1 33	
3 "	2207	9	3 93		811	1	4 03	
4 "	2251	4	1 77		811	1	4 03	

The technique adopted was to place about 1 gramme of faeces in a 1-ounce screw-capped vial two-thirds full of sterile broth. This was thoroughly shaken and left in the refrigerator overnight. The supernatant fluid was then centrifuged until quite clear when a quantity was pipetted off and heated to 58° C. for 30 minutes. This was tested for bacteriophage content against *B. dysenteriae* Shiga and Flexner.

In all, thirty two specimens were tested of which twelve were taken the morning after treatment started, *i.e.* the second day of the illness, and ten on each of the 3rd and 4th days. In some cases the specimens consisted of blood and mucus only in others they had taken on a faecal character. From all thirty two specimens active bacteriophage was readily recovered.

One specimen prepared as above recovered from a 4th-day sample, was diluted and tested against *B. dysenteriae* Shiga. It produced complete lysis by the patch technique in a dilution of 1/100.

In thirteen cases, bacteriophage action was observed in the colonies on the original MacConkey plate from which the isolation was made. Such colonies had a nibbled edge or were crescentic in shape. In association with these another appearance was noted a pitting of the surface, making the colony granular and more opaque looking. In one case the bacteriophage action was so marked that all the dysentery colonies disappeared from the plate after it had been left on the bench for some time.

From these tests it can be concluded that bacteriophage given orally in the above doses reaches the bowel and is present in the stools in an active condition and in considerable quantity.

Specimens were taken from thirteen of the control series on the 4th morning and extracted by the technique detailed above. No bacteriophage was detectable in the undiluted extract.

(*c*) *Details of Treatment in Control Series*

All cases were admitted to hospital on the first sign of blood and mucus in the stool.

Standard saline treatment was given to all cases—sodium sulphate in 1 drachm doses three times on the 1st day and thereafter as indicated by the patient's condition. Cases which failed to respond or showed severe symptoms were put on treatment with one or other of the sulphonamide drugs. Three cases in the control series had to be treated in this way.

Diet consisted of fluids only (not milk) the 1st day with subsequent addition of small quantities of toast, fish, etc. as warranted by the patient's condition.

(*d*) *Details of Treatment in Bacteriophage Series*

The medical officer and N.C.O. in charge of each cage were given careful instructions on the procedure to be followed.

Every man with symptoms of diarrhoea no matter how slight was ordered to report to the cage medical inspection room immediately Here he was at once put on bacteriophage therapy and his diet restricted to tea and if he wanted it bread A complete course of bacteriophage treatment was thereafter carried through irrespective of his further progress

This consisted of —

1st day	Ruhr Bakteriophagen	15 c c three times daily
2nd day		15 c c.
3rd day		10 c c

If symptoms were severe and in any case on the first appearance of blood and mucus in the stool, the patient was admitted to hospital where treatment as detailed above was continued until the course was completed No other drugs were administered during the bacteriophage course unless the severity of the symptoms demanded further intervention. Four cases in the bacteriophage series had to be placed on sulphonamide therapy

The diet in these cases was the same as in the control cases—fluid until the symptoms abated

1 Prophylactic Action of Bacteriophage

Claims have been made (Kliewe and Helmreich 1941) that the administration of dysentery bacteriophage confers immunity against this disease for some considerable time

An attempt was made to confirm this claim, but the low incidence of dysentery during the experiment somewhat vitiated its value

One cage was selected, and records of strength and dysentery incidence were kept for 4 weeks. Each inmate of the cage was then given 10 c.c of bacteriophage on a fasting stomach on three successive mornings, and observations were continued for a further period of 4 weeks All newcomers to the cage, after the date of the mass bacteriophage administration, were given a 3-day course immediately on arrival. Table IV shows the weekly figures before and after together with figures from three untreated cages selected as controls

No cases occurred while the bacteriophage was being administered, but this is of no significance, as four similar blank periods of 3 days or more occurred in the preceding 6 weeks One case occurred the day after the prophylactic treatment ceased and two others on the 3rd day after the cessation of treatment.

The evidence so far as it goes gives no indication that bacteriophage is capable of conferring immunity against dysentery infection for any length of time In fact although the incidence among the treated personnel was lower in the 4 weeks following the administration of bacteriophage than it was in the preceding 4 weeks, it remained higher than in the controls The number of cases is however so small that the figures are erratic and only general conclusions can be drawn.

2. Effect of Bacteriophage in Aborting Bacillary Dysentery

In Table V the figures relating to this aspect of the investigation are given. The salient points to be noted are —

(*a*) The numbers at risk are considerable

(*b*) The numbers reporting sick in the test series are higher than in the control series. This may be explained by the fact that medical officers and orderlies in the cages selected for bacteriophage treatment were instructed to be on the look out for cases of diarrhoea so that treatment could be started at the earliest moment. It seems probable that in following these injunctions, cases were included in the series which would have passed unnoticed in the control cages where normal procedure was in vogue

(*c*) The percentage of men who developed clinical dysentery and were admitted to hospital is almost identical in both the control and the bacteriophage-treated groups, *i.e.*, 2·96 and 3·1 respectively

(*d*) It would therefore appear that bacteriophage even when administered in large doses at the earliest symptom, is incapable of aborting an attack of bacillary dysentery

Table V

Incidence of diarrhoea and clinical dysentery in the control and test groups, from 10th May 1943, to 9th July 1943 (61 days).

	Control Group.	Bacteriophage Treated Group.
Daily cage strength of group	4,890	4,0 0
Total number with symptoms of diarrhoea	493	34
Percentage of number at risk who developed symptoms of diarrhoea %	6·18	8 ..
Number of cases of clinical dysentery admitted to hospital	134	126
Percentage of number at risk who were admitted to hospital	·96	3·1

3. Effect of Bacteriophage in Modifying the Course of an Attack of Bacillary Dysentery

An assessment was made of the severity of each case on admission to hospital, while data were kept of the time taken for blood and mucus to disappear from the stools, and of the length of stay in hospital. Although these criteria give only limited information, they provide a general indication of the progress of the case of sufficient accuracy to show up any gross variations.

The results are shown in Table VI on which the following comments are made.

TABLE VI

COMPARISON OF CONTROL CASES AND BACTERIOPHAGE TREATED CASES. (CLINICAL DYSENTERY)

		Control Group	Bacteriophage treated Group
Number of cases analysed		126	124
Assessment of severity on admission	Percentage mild	75·4	83 74
	" moderate	18 25	12 90
	" severe	6 35	3 36
Average number of days for blood and mucus to disappear		9·03	9·08
Average stay in hospital (days)		19 83	16 97

(*a*) *Number of Cases*

The seven cases placed on sulphonamide treatment are excluded for obvious reasons, as are also six others regarding whom adequate data are not available. Yet another case proved to be a mixed infection of bacillary and amoebic dysentery Two cases among medical personnel, not included in Table VI because they were not inmates of the cages under observation, are included in the bacteriophage treated group in Table VII

(*b*) *Severity on Admission.*

The degree of severity was assessed on the condition of the patient at the time of admission. The number of stools, amount of blood and mucus, temperature and pulse rate and the general appearance of the patient were taken into consideration.

The difference between the cases in the two series was not striking but the balance was slightly in favour of the bacteriophage-treated group This may have been due to the action of the bacteriophage already administered but in view of the fact that living organisms were readily recovered from the stools at this stage such an explanation must be accepted with caution. In fact, the difference was more marked in the early stages of the investigation and became less noticeable as the number of cases in both series increased. It is possible that it would have disappeared completely if the investigation had been sufficiently extended.

(*c*) *Average number of days taken for Blood and Mucus to disappear from the Stools and Average Stay in Hospital*

Figures for all cases of clinical bacillary dysentery are in Table VI and grouped according to the infecting organism in Table VII

The over-all average time before blood and mucus disappeared from the stools was very similar in both series. When analyzed according to the infecting organism, it is seen that there is little difference in Flexner infections, but a

TABLE VII.

ANALYSIS OF ISOLATIONS OF DYSENTERY BACILLI SHOWING AVERAGE TIME FOR BLOOD AND MUCUS TO DISAPPEAR, AND LENGTH OF STAY IN HOSPITAL.

	Control Series.			Bacteriophage Series.		
	Number of Cases.	Average Days till B./M. Negative.	Average Days in Hospital.	Number of Cases.	Average Days till B./M. Negative.	Average Days in Hospital.
B. dysenteriæ						
Flexner	39	8·84	19	48	8·9	17·47
Shiga	50	17·35	28·5	14	14·86	23·0
Schmitz	8	1·0	22·0	10	6	14·7
Sonne	4	3·0	20·0	—	—	—
Non-mannit fermentor	—	—	—	1	8·4	16·0

slight balance in favour of bacteriophage-treated cases in Shiga infection. The numbers involved in the other groups are too small to be of significance.

In Table VIII an assessment is made of the same particulars in those cases in which bacteriophage action was observed in the colonies on the original plate from which the organism was isolated. Presumably these are cases in which much bacteriophage was present. The averages in this group (admittedly open to criticism because the numbers are small) show no significant variation from the averages in the control series.

TABLE VIII.

ANALYSIS OF CASES IN WHICH BACTERIOPHAGE ACTION WAS NOTED IN THE COLONIES ON THE MCCONKEY PLATE.

Type.	Number of Cases.	Severity.	Average Number of Days until Blood and Mucus Negative.	Average Number of Days in Hospital.
Flexner	7	Mild	9·4	19·3
Shiga	4		17·3	27·8
Schmitz			6·5	13·0

The average stay in hospital was less in the bacteriophage treated cases than in the controls. A noteworthy feature is the undue length of this period in both series. It is considerably greater than is found necessary in British hospitals, and under British medical officers.

To summarize, it may be said that bacteriophage treatment produced no dramatic results in modifying the severity or duration of the attack. The slight balance in favour of the bacteriophage group might well have been levelled out in the course of a more extended observation.

LABORATORY ASPECTS OF BACTERIOPHAGE THERAPY

(*a*) *Effect of Bacteriophage on the Isolation of Dysentery Bacilli from Faeces*

The isolations of dysentery bacilli details of which are in Table II were disappointingly low. Specimens were selected by the German medical officers or orderlies placed in small vials of glycerine saline solution, and sent to the laboratory for plating. The laboratory was some little distance outside the hospital enclosure and it was not feasible to send freshly passed stools in the bedpan. The isolation rate is considerably lower than that obtained by the same laboratory from outlying British units (78 per cent.) where a similar technique was used. The most probable explanation is that sufficient care was not exercised by the German personnel in the collection of suitable fresh specimens.

The percentage of isolations is very similar in both series—50 per cent. in the control and 55·5 per cent. in the bacteriophage-treated series. It has already been shown that bacteriophage is present in the faeces of treated cases on the morning following its exhibition and persists throughout the treatment. Table IX. shows the days on which isolations of dysentery bacilli were obtained. It will be seen that the presence of bacteriophage in the faeces did not appear to lessen the chances of isolating the dysentery bacillus, despite the fact that *in vitro* the strains were found to be susceptible to its action.

TABLE IX.

DAY ON WHICH DYSENTERY BACILLI WERE ISOLATED FROM THE STOOLS.

Series	Number of Cases in which Dysentery Bacilli were first Isolated on			
	Day of Admission to Hospital	Day following Admission to Hospital.	2nd Day following Admission to Hospital.	3rd Day following Admission to Hospital.
Control series	31	32	4	1
Bacteriophage series	19	41	9	1

Note.—1. The days in the Table are those on which the specimen was passed.

2. Bacteriophage was always given on the day of admission, and may have been given 1 or 2 days earlier.

(b) Further Experiments

Further experiments were carried out to obtain more specific data on some of these points.

A healthy volunteer swallowed 2 doses of 50 c.c. of Ruhr Bakteriophagen at an interval of 12 hours. Bacteriophage was present in his stools the next morning, and remained in diminishing concentration for 6 days after which it could not be detected by the technique detailed above

The same volunteer on a subsequent occasion swallowed 100 c.c. of bacteriophage, and 6 hours later a specimen of blood was taken. Bacteriophage was present in the serum in a concentration which, using the patch technique, gave complete lysis in a dilution of 1 in 1000

Specimens of urine were examined after 3 6, 9 and 24 hours. Bacteriophage was absent from the 3 hours specimen, present in the 6 hours specimen, and absent from all later specimens.

Another volunteer repeated this experiment with the following results

Hours	Serum contained bacteriophage giving complete lysis
After 3	in a dilution of 1/100
6	" " 1/1000
" 14	" " 1/10
24	Not demonstrable.

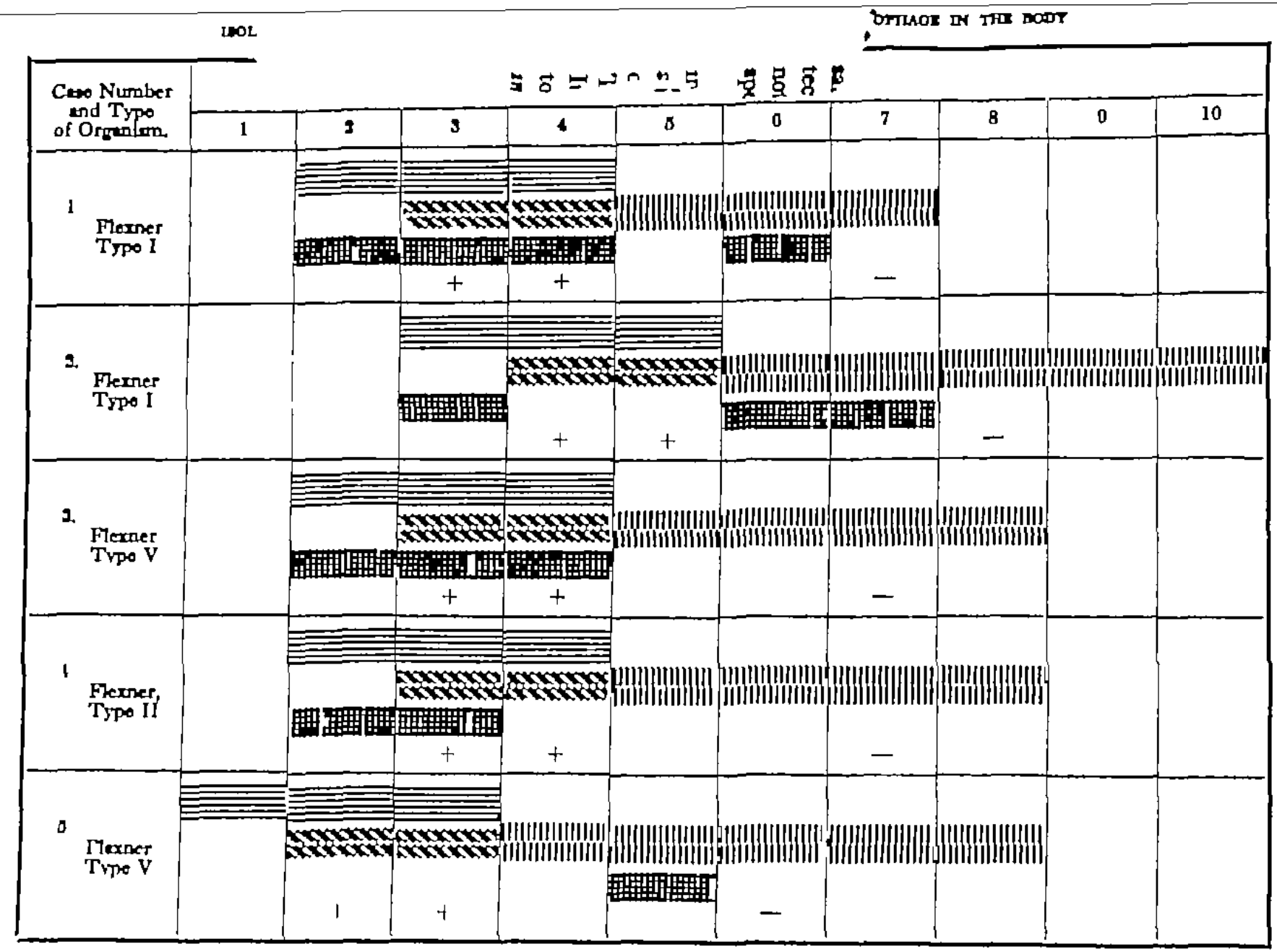
Thus it would appear that when bacteriophage is swallowed some of it quickly absorbed and reaches its highest level in the blood in about 6 hou Within 24 hours it is no longer to be detected in the blood, having been excre and possibly in part destroyed by the tissues.

It is present in the stools on the morning after administration, and persi for at least 6 days.

Five mild cases of bacillary dysentery in a British hospital were select and treated for 3 days with 15 c.c. of Ruhr Bakteriophagen three times dail The stools were examined repeatedly for the presence of bacteriophage ar dysentery bacilli, and the serum was tested for bacteriophage 24 48 and 12 hours after the beginning of treatment.

The results are shown in the diagram. They illustrate the persistence of bac teriophage in the stools, and the simultaneous presence of dysentery bacilli In Cases 1 2 and 5 the infecting organism was recovered after bacteriophag had been present in the bowel for 4 days, in Case 3 after 2 days, and in Case 1 after 1 day All the organisms were readily susceptible to the action of the bacteriophage.

It is noteworthy that bacteriophage persisted as long in the stools of the normal volunteer as it did in the stools of patients suffering from bacillary dysentery There is thus nothing to suggest multiplication of the bacteriophage in the presence of its specific pabulum in the bowel.


ISOL
DISTANCE IN THE BODY
Case Number and Type of Organism.
1
2
3
4
5
6
7
8
9
10
1 Flexner Type I
2. Flexner Type I
3. Flexner Type V
1 Flexner, Type II
5 Flexner Type V
+
—
= Bacteriophage 15 c.c. t.d.s. by mouth.
= Bacteriophage present in stool
= Bacteriophage content of stool not tested but shown by previous experiments to be invariably present at this stage
= Organism isolated from stool.
+ } = Bacteriophage present or absent in blood stream.
—

Discussion

From the results obtained in these "field" trials only one conclusion can be drawn, namely that specific bacteriophage administered orally has no prophylactic action in bacillary dysentery, is incapable of aborting an attack of the disease and has no dramatic effect, if indeed it has any action at all, in modifying the severity and duration of an attack.

These findings are in keeping with those of most observers who have checked their results by maintaining controls and differ only in that, on account of the unique opportunity which offered itself, it has been possible to make the investigations under realistic conditions ideal both for control and observation. They are sadly at variance with those which might be expected from a study of the *in vitro* behaviour of bacillus and bacteriophage. The latter is a spectacular phenomenon, and there is little wonder that it has given rise to high hopes for bacteriophage as a therapeutic agent.

In seeking an explanation of the failure of bacteriophage to produce beneficial results, there are several points to which due consideration must be given.

(*a*) The potency of the bacteriophage against the dysentery group of bacilli as a whole and against the various strains identified in this experiment has been definitely demonstrated.

(*b*) There can be no doubt that the bacteriophage reaches the seat of the disease. When taken orally it appears to be partly absorbed during its passage through the upper bowel, is found in the blood stream with a maximum concentration within 12 hours of ingesting, and thereafter falls off rapidly disappearing within 24 hours. It is excreted in the urine for a brief period which in the one case tested lay between the 3rd and 9th hour. It is probable that the bulk of the bacteriophage passes unchanged into the large intestine, for it can be detected in the faeces in a considerable concentration for from 5 to 7 days after administration, both in the normal subject and in the patient suffering from dysentery. Thus the bacteriophage has an opportunity to act on the bacilli in the bowel wall both through the blood stream and locally from the lumen of the colon.

In his experiments, Rudno (1930) failed to detect bacteriophage in the stools of his treated cases, and concluded that it had been eliminated or destroyed. It seems more probable that the technique he used was not sufficiently delicate to pick out the relatively small quantity he used.

(*c*) Living dysentery bacilli can readily be recovered from stools in which a considerable concentration of bacteriophage is present—witness the fact that isolations were as numerous in the treated series of cases as in the controls. Further, they continue to occur for periods up to

4 days after the bowel contents have become saturated with bacteriophage

The simultaneous presence in the stools of susceptible dysentery bacilli and bacteriophage, lasting for periods up to 2 weeks has already been demonstrated by WHEELER and BURGDORF (1941)

(*d*) As gauged by the macroscopic and microscopic characters of the exudate the inflammatory process in the bowel wall pursues the same course in the bacteriophage treated cases as it does in the controls There is nothing to suggest that it is in any way modified in the former

RIDING (1930) has shown that bacteriophage action is slowed down if not inhibited in the presence of mucus, and concludes that the contents of the intestine in dysentery do not seem to be a suitable medium for bacteriophagy This however is not the whole story To be effective bacteriophage must act, not only on the organisms in the lumen of the bowel, but also on those in the superficial layers of the bowel wall where they are propagating The facts elicited above indicate that this does not occur and that instead of being rapidly destroyed and eliminated the pathogens in the bowel wall continue to multiply and produce their usual reaction and are shed in a living state into the lumen of the bowel in the exudate which characterizes the disease.

All evidence goes to show that the clear-cut reaction which takes place between bacillus and bacteriophage under experimental conditions in the laboratory does not occur in the human body In its absence, it is idle to expect that bacteriophage therapy will have any effect on the development or course of the disease

No explanation is offered as to why bacteriophage fails to act *in vivo* The subject is a complex one which calls for much detailed investigation.

It is worthy of note that these conclusions on the action of bacteriophage in the treatment of dysentery in the human being are in close conformity with those made by TOPLEY *et al* (1925) on the effect of bacteriophage in *B aertrycke* infections in mice These authors after detailing some carefully controlled experiments state The observations we have recorded do not suggest that the presence of the bacteriophage will in itself prevent the epidemic spread of infection, check an epidemic when it has started or appreciably reduce the mortality among the population at risk. A further experiment by TOPLEY and WILSON (1925) showed that intraperitoneal inoculation of a lytic filtrate was no more effective than oral administration. COMPTON (1928) also found that the treatment of experimental plague by subcutaneous injection of a weak phage after infection is without any curative effect.

SUMMARY

1 An investigation into bacteriophage therapy in bacillary dysentery was carried out in circumstances which permitted of accurate control

2. The bacteriophage used was of high potency It was specific for the

dysentery organisms isolated. It was recovered from the stools of patients to whom it was administered.

3 No prophylactic action was found to result from a 3-day administration of bacteriophage along the lines recommended by KLIEWE and HELMREICH.

4 The incidence of dysentery in a community treated with bacteriophage at the first sign of diarrhoea was no different from that in a control community

5 Neither the severity nor the duration of the attack in the bacteriophage-treated group was dramatically less than in the controls.

6 Dysentery bacilli were recovered from the stools after the bowel had been exposed for as long as 4 days to the action of bacteriophage

7 It is concluded that bacteriophage fails to exercise *in vivo* the potent properties which it exhibits *in vitro*

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SEROLOGICAL EXAMINATION AND A CUTANEOUS TEST IN THE DIAGNOSIS OF BACILLARY DYSENTERY

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Considerable difficulties exist with regard to the laboratory diagnosis of bacillary dysentery Their source is commonly known to be the outstanding sensitivity of the bacilli to environmental conditions, their brief viability when exposed to light, cold, traces of urine or disinfectants especially in stools where the presence of bacteriophage represents a continuous danger to their existence. Thus the time passing until cultivation is performed, the distance of the laboratory the choice of suitable portions of the dysenteric stool the climatic conditions are some of the factors which may influence the result of the bacteriological examination. Attention has therefore been paid to obtaining the specimens at the patient s bedside and culturing them at once. By taking dysenteric exudate directly from the bowel by a rectal swab or by rectoscopy positive results are more frequently obtained. Nevertheless, the difficulties are still great especially in cases of chronic bacillary dysentery where the percentage of negative cultures is notoriously large in Rogers s (1929) opinion a positive culture is exceptional in those cases Therefore a number of diseases of the bowels caused by chronic dysenteric infections are certainly misdiagnosed for lack of confirming bacteriological evidence.

Also the clinical diagnosis of dysenteric disorders has its fallacies, indeed more in chronic than in acute dysentery Acute bacillary dysentery it is true is generally diagnosed as such and not commonly confounded with other acute diseases of the gastro-intestinal tract. Chronic bacillary dysentery on the other hand, represents a difficult problem especially because of its protean nature simulating very different diseases of the intestine.

The exact diagnosis of bacillary dysentery however is of definite importance since modern chemotherapy particularly sulphaguanidine, and, to a

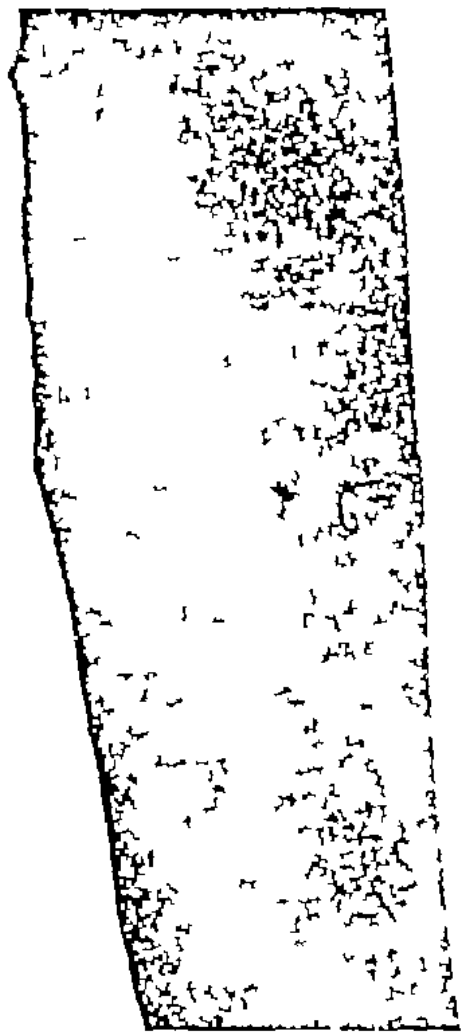
certain extent, vaccinotherapy are very efficient in the treatment of those cases and, as we are inclined to assume only of those cases As are the results of specific chemotherapy spectacular in suitable cases, so are they poor in other dysenteriform conditions of the bowels.

It is evident, therefore that the diagnosis of bacillary dysentery should be improved by all available means. The search for additional diagnostic procedures led to the use of the agglutination test especially in cases of long duration. The finding of agglutinins does not seem to be so constant in the serum of patients ill with bacillary dysentery as it is in other infectious diseases a fact which may be explained by the lack of bacteriaemia in this disease compared, for example, with the enteric fever group or brucellosis. A survey of the literature on the subject reveals different opinions concerning the diagnostic value of these agglutinins. MANSON-BAHR (1939) and BOYD (1940) are somewhat sceptical about the evaluation of this examination—the former calling it an " unstable weapon in bacillary dysentery and stressing the finding of agglutinins in some normal serums. BOYD points out the difficulties encountered because of the diversity of the paradysentery organisms and describes an elaborate technique to avoid pitfalls in serological diagnosis. MANSON BAHR describes the behaviour of agglutinins he appreciates a positive finding particularly in the detection of carriers and, in a recent article, emphasizes its usefulness in the diagnosis of chronic cases. He regards a titre of 1 40 as diagnostic for Shiga infection and of 1 100 for the paradysentery group TOPLEY and WILSON (1934) think that complete reliance should not be placed on the demonstration of agglutinins in the diagnosis of dysentery A titre of 1 40 is highly suggestive of a Shiga infection whil a titre of 1 150 for Flexner in the absence of Shiga and typhoid agglutinins is suggestive of a Flexner infection this being partly confirmed by a rise and fall in the agglutinin curve Agglutinins are said to decline shortly after convalescence and to disappear within three months after infection except in cases of chronic carriers where they may persist for much longer CRUICKSHANK and SWYER (1940) mention the serological examination as an aid which proved to be valuable in an outbreak of Sonne dysentery MUHLENS RUGE and ZUR VERTH (1930) quote the opinions of several authors who deny any value in this method, whereas they themselves consider the examination as a method which can be used to advantage especially in differential diagnosis against amoebic dysentery SCHITTENHELM (1925) gives about the same diagnostic titres as MANSON BAHR (1942) he even compares its usefulness with that in typhoid, when used with the necessary caution. BLATT and SHAW (1938), in a survey of bacillary dysentery in children, felt that the procedure probably was reliable and should be tried further "

We have used the agglutinin determination in twenty five bacillary dysentery patients, acute and chronic, and in forty-three control cases with various dysentery like and other diseases. We have considered 1 100 and more as a

positive result in Flexner infection especially when former examination revealed a lower titre in the only case of Shiga infection a titre of 1 50 was found. Our purpose was further to evaluate the usefulness of this procedure as a diagnostic measure in bacillary dysentery and at the same time observe the behaviour of these agglutinins

With regard to the contradictory opinions on the value of the agglutination test and the difficulties mentioned above which are encountered in



routine laboratory diagnosis an additional method was devised by one of us (F D) in the attempt to provide the clinician with another diagnostic method in bacillary dysentery (Flexner) BROKMAN in 1923 had worked out a test for diagnosing Shiga dysentery by administering Shiga toxin intracutaneously In a similar way to Schick s test in diphtheria a negative reaction shows the presence of antibodies and is therefore diagnostic of previous Shiga infection. Similarly our method represents a test of cutaneous sensitivity to Flexner vaccine and a positive response is regarded as an expression of preceding

infection We also used Strong vaccine in a good many cases but when it became clear that nearly always both Flexner and Strong tests showed the same results we have lately abandoned the use of Strong vaccine.

Of a vaccine containing 50 million bacilli in 1 c.c., 0 1 c.c. is administered intracutaneously in the forearm. Infiltration and redness sometimes quite considerable, exceeding 3 to 4 cm. in diameter were usually present in cases of Flexner infection whereas slight reddening of the skin and mild infiltration occurred to a lesser extent in a good many cases even when there was no suspicion of a previous Flexner infection A mild or doubtful cutaneous reaction should therefore, usually be regarded as negative. The appraisal of the result may consequently require a certain experience as in all kinds of tests for cutaneous sensitivity As in agglutination tests a mild response even when not very pronounced should be considered as suggestive or even positive when previous examinations revealed a completely negative result. A typical positive reaction is to be seen in the picture. The local reaction is sometimes rather intense but besides slight pain or itching no undesirable reactions have been observed. The reaction appears about 12 hours after injection and becomes distinctly positive in suitable cases after 24 hours. This test has been employed in most of the following cases and has in our opinion proved its usefulness. It becomes positive when performed about a week after the onset of infection It has not yet been definitely ascertained how long the positive reaction persists after the infection has subsided.

In most cases single or repeated bacteriological and serological examinations, as well as cutaneous tests, have been performed in order to establish changes in titre The agglutination test has been repeated several times in nearly every case. Most of the cases were diseases of the intestines, but a few cases of other pathological conditions have been used as controls The most suitable control series for such an examination is of course amoebiasis.

BACILLARY DYSENTERY

Twenty six cases of typical bacillary dysentery were examined, fifteen gave positive Flexner cultures one a Shiga culture while the other ten showed the typical picture and course of bacillary dysentery but gave negative stool cultures sometimes probably because they came under observation too late In twenty-one cases the agglutination test was positive and in twenty one cases the cutaneous test in seventeen of them both were positive. The agglutination test was negative in one case in an old cachectic patient, 70 years old once when taken a few days after childbirth once when taken only 3 months after the acute illness once it had a doubtful result when taken only a week after the onset of the disease (1 100 ±) One case must be considered a failure of the method. The cutaneous test was negative in one case of this disease in an old man, aged 72, in a cachectic state it was not employed in one case because of a complicating diffuse eczema it provided a doubtful result in a case of

carcinoma of the stomach with anaemia, complicated by acute bacillary dysentery whereas the agglutinin response was quite normal its result was doubtful, too in a case of uraemia and severe exhaustion and loss of weight following acute bacillary dysentery the result was negative and therefore possibly a failure in a short attack of acute clinical dysentery

GASTRO-ENTEROCOLITIS.

This is a less homogeneous pathological entity than bacillary dysentery Twelve cases were examined. The agglutination test was negative in 8 cases, the cutaneous test in 9 in 7 of them both the serological and cutaneous tests were negative The serological examination was positive in one patient who had had an attack of dysentery 2 years earlier in another who had had several attacks of diarrhoea with fever but in whom no dysentery bacilli had been found one who had prolonged febrile diarrhoea of an unknown origin and was examined in the first month of pregnancy after the diarrhoea had already ceased In the last case the cutaneous test was also positive. A doubtful result was obtained in both tests in a case of chronic gastritis of which no history could be taken because of language difficulties and a previous infection could therefore, not be excluded.

AMOEBIASIS OF THE INTESTINE.

Eight cases were examined all confirmed by examination of the stools. The serological test was negative in all but one case. This case, a young girl, was suffering from a chronic dysenteric disorder The response to the usual specific treatment (emetine + chardyl) was extremely poor and the possibility of a double infection—amoebic and bacillary—could not be excluded. The cutaneous test was not performed in two cases, in the other six it was negative.

SPASTIC COLON

The agglutination test was negative in five cases the cutaneous test in four In four out of the five cases of typical spastic colon both tests gave negative results. In one case both were positive the patient had had bacillary dysentery four years earlier and since then she had several times suffered from diarrhoea.

ULCERATIVE COLITIS.

Seven cases were examined. In one the cutaneous test was not performed. In one case of this group where a typical ulcerative colitis had been present for many years and many negative results had been obtained in stool examinations, cultures showed Flexner in three consecutive examinations during 2 days. In all subsequent cultures negative results were obtained. The transient Flexner infection did not produce any change in the clinical picture The agglutination test had been negative one day after the bacillus had been cultured and the

titre reached 1 200± a week later Two cutaneous tests supplemented by a test performed with the strain of Flexner bacillus obtained from the patient s stools were negative. In a similar case of ulcerative colitis, where the Flexner bacillus was obtained only once during a rectoscopic examination, the patient had presented the typical features of chronic ulcerative colitis for many years The agglutination test was positive for a short while (3 to 4 weeks) and then the titre, which had increased from 1 50 to 1 100 disappeared completely The cutaneous test was negative. In both these cases, in our opinion, the Flexner infection was most probably an accidental complication of a pre-existing ulcerative colitis, an argument which is sustained by the patient s history findings subsequent course and response to treatment. One case, a man aged 70 who developed acute severe entero-colitis with sanguinolent diarrhoea and ulcers in the bowels was well influenced by sulphaguanidine The agglutination test was negative whereas the cutaneous test was positive. Bacillary dysentery could not be excluded.

VARIOUS DISORDERS

When examined in widely varied disorders (pellagra, hypertension duodenal ulcers and other conditions) of eleven cases the agglutination test was positive in only one, a case of hypernephroma with anaemia. In this case no explanation could be found and it has to be regarded as a failure of the method The cutaneous test—for technical reasons—was made only three times in this group and was negative in a case of hypertension one of hypernephroma and one of intestinal tuberculosis

It may be concluded that one or both tests were negative in a few cases where a positive result should have been expected This happened especially in patients who were in a very run-down and cachectic condition, in advanced age, or in pregnancy With these exceptions and some rare unexplained failures mentioned above both tests proved their usefulness In some cases one of the tests might have led to a mistaken diagnosis (false positive or false negative) if the result of the second test together with all the history findings and clinical evidence had not indicated the right diagnosis Sometimes these combined examinations may serve as a means to detect a carrier as has already been emphasized by several authors for the agglutination test. In one case (S A) where the diarrhoea and all clinical symptoms had completely disappeared a few weeks earlier an agglutination titre of 1 100 Flexner and a strongly positive cutaneous test drew our attention to a previous dysenteric infection. A culture was taken of material obtained by rectoscopy which promptly revealed a Flexner infection and thus adequate treatment with sulphaguanidine was given.

We observed, in conformity with previous workers that the agglutinins usually appear about 7 to 10 days after the onset of infection and the cutaneous test behaves in the same way The agglutinins disappear from the blood after

various time intervals, weeks or several months, whereas a positive cutaneous test seems to have a tendency to persist for a longer period. The agglutinins did not reach a titre higher than 1 200 in any case and frequently only 1 100 but we have frequently observed the typical rise in agglutinin titre during the course of infection (0 1 50, 1 100)

In bacillary dysentery the determination of blood agglutinins and a test of cutaneous sensitivity to Flexner vaccine as described above seem to provide valuable information for the diagnosis of this condition. These examinations are indicated in cases where infection with bacillary dysentery is suspected and cannot, or can only with the utmost difficulty be confirmed by the usual means available for clinical and laboratory diagnosis. Although neither of the two tests can be compared with the certainty of the Widal-reaction in typhoid they seem to be useful when evaluated together with the clinical picture of the disease

Summary

The difficulties in laboratory and clinical diagnosis of bacillary dysentery and, on the other hand, the desirability of an exact diagnosis in those conditions, are stressed

A short survey of the literature of the agglutination test in bacillary dysentery is given. The behaviour of these agglutinins is briefly discussed. A method of testing the sensitivity of the skin against dysentery bacilli is described and both methods besides the usual diagnostic means applied in a mixed group of 69 cases, among them 26 of bacillary dysentery

Both procedures seem to have proved their usefulness as aids in the diagnosis of dysenteric disorders.

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PENTAMIDINE IN THE PREVENTION AND TREATMENT OF TRYPANOSOMIASIS

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I. PENTAMIDINE IN TREATMENT

A. RATE OF DISAPPEARANCE OF PARASITES FROM THE PERIPHERAL BLOOD

In guineapigs infected with *Trypanosoma gambiense* and treated with a single dose of 0·002 to 0·003 gramme per kg., the time before the complete disappearance of the parasites in the peripheral blood was at least 41 hours and in some cases slightly more than 54 hours. In sleeping-sickness patients the trypanosomes were still detected 48 hours after a single dose of 0·002 gramme per kg. But, as a rule the parasites are no longer present in the blood and the gland juice on the 3rd day after this average dose.

B. INTERVAL OF ABSENCE OF TRYPANOSOMES FROM BLOOD AFTER SINGLE DOSES.

This experiment was made on guineapigs infected with various strains of *T. gambiense*. The date of injection was delayed for several days after the first spontaneous trypanolytic crisis, that is until the disease was firmly established.

* We are indebted to Messrs. May & Baker for adequate supplies of pentamidine (May & Baker 800) for the purpose of this investigation.

various time intervals, weeks or several months, whereas a positive cutaneous test seems to have a tendency to persist for a longer period. The agglutinins did not reach a titre higher than 1 200 in any case and frequently only 1 100, but we have frequently observed the typical rise in agglutinin titre during the course of infection (0 1 50 1 100).

In bacillary dysentery the determination of blood agglutinins and a test of cutaneous sensitivity to Flexner vaccine as described above seem to provide valuable information for the diagnosis of this condition. These examinations are indicated in cases where infection with bacillary dysentery is suspected and cannot, or can only with the utmost difficulty be confirmed by the usual means available for clinical and laboratory diagnosis. Although neither of the two tests can be compared with the certainty of the Widal-reaction in typhoid, they seem to be useful when evaluated together with the clinical picture of the disease

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A short survey of the literature of the agglutination test in bacillary dysentery is given. The behaviour of these agglutinins is briefly discussed A method of testing the sensitivity of the skin against dysentery bacilli is described and both methods besides the usual diagnostic means applied in a mixed group of 69 cases, among them 26 of bacillary dysentery

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For both patients this dosage had been calculated at 1 mg to 3 mg of the drug per kg body weight injected intramuscularly

The second patient presented marked symptoms of intolerance for the drug Treatment was interrupted after the fifth injection, and followed by a few injections of tryparsamide and Bayer 205

Final result was the clinical cure and a normal cerebrospinal fluid ten cells, 0·22 o/oo albumin, globulin test negative

2 *Advanced cases with clinical and cerebrospinal signs of encephalo-myelitis not yet treated with other drugs*

A —Injection twice weekly on an average of 1 to 2 mg per kg body weight

Case 1 S M.—C.S.F 124 cells 0 56 o/oo albumin, globulin test = ++ Injected twice weekly 0·05 gramme 4 × 0 10 gramme intravenous and 5 × 0 1 gramme intramuscular The drug was well tolerated, the clinical result not appreciable but the cell count in the lumbar fluid was better 31 cells, 0 56 o/oo albumin, globulin test dubious

The patient was treated later with tryparsamide and antrypol and she did not improve

Case 2 J B —C.S.F 310 cells, 0 71 o/oo albumin, globulin test = ++ Same plan of treatment for a total dose of 0·96 gramme pentamidine. Lumbar puncture after this treatment 145 cells albumin increased to 0·85 o/oo globulin test still ++

A second puncture 1 month later 608 cells 0·65 o/oo albumin Clinically worse but the trypanosomes had disappeared

Case 3 A. E.—A similar case. C.S.F 110 cells 0·4 o/oo albumin globulin test ++ Doses of 0·06 gramme 0 1 gramme (which was badly tolerated) 0·05 gramme and 0·025 gramme. These last injections provoked marked signs of intoxication. The treatment had to be interrupted and at that time the C.S.F showed 395 cells 0 56 o/oo albumin. No more trypanosomes in the blood and enlarged lymph glands

Case 4 A. K.—C.S.F 312 cells 1 13 o/oo albumin and many trypanosomes Injected in the muscle twice a week 0 1 gramme of pentamidine total 1 gramme. Drug well tolerated. There was a slight clinical improvement and after this treatment the fluid showed 130 cells 0·85 o/oo albumin and a high positive globulin test.

Case 5 A. I —A case to be compared with the previous one After a total of 1 gramme pentamidine the patient was still in poor condition cell-count in the C.S F had increased from 242 to 313 albumin unchanged at 0 56 o/oo

Case 6 G E —Very advanced case with 402 cells 0 7 o/oo albumin and numerous trypanosomes in the C.S.F A course of treatment with a total dose of 1 22 grammes pentamidine did not improve either the clinical symptoms nor the C.S.F However no more trypanosomes were observed and the albumin rate had decreased from 0 7 o/oo to 0 56 o/oo

B —Injections at short intervals up to the limit of tolerance

Case 7 A. A.—Very advanced case complicated with syphilis Insane. C.S.F 142 cells 0 71 o/oo albumin Weichbrodt test ++ Wassermann negative in the C.S.F and positive in the blood Injected daily 22 × 0·03 gramme, 2 × 0·04 gramme 5 × 0·05 gramme. This total of 0·99 grammes was fairly well tolerated. C.S.F after treatment 85 cells 0 71 o/oo albumin Weichbrodt ++ Clinically unchanged. Trypanosomes no longer found in the blood.

Case 8 M M.—A late case of sleeping sickness with all the classical symptoms C.S.F 1 680 cells 0 71 o/oo albumin, Weichbrodt test ++ trypanosomes present in blood and glands

Injected daily 15 × 0·04 gramme 12 × 0·05 gramme in all 1 2 grammes pentamidine After this treatment, which was well tolerated and did not give later any signs of delayed intoxication the C.S.F showed 765 cells 0 56 o/oo albumin and *numerous free*

trypanosomes. However trypanosomes were no longer to be found in the blood nor in the enlarged lymph glands.

3. *Advanced cases formerly treated without success with various drugs*

Case 1. M. S.—Was an advanced case with 685 cells 0·48 o/oo albumin and trypanosomes in the cerebrospinal fluid, when he received a course of 10 × 2 grammes tryparsamide 8 × 0·5 gramme tryatibine a third of 2 grammes only tryparsamide and 6 × 0·5 gramme tryatibine and finally 14 injections of 1 gramme tryparsamide.

He was better for a short time but relapsed clinically after 6 months, and was treated with pentamidine.

Before treatment the C.S.F showed 707 cells 0·71 o/oo albumin, globulin test ±. After 0·50 gramme, 0·60 gramme 2 × 0·2 gramme 6 × 0·1 gramme the cerebrospinal examination gave the following result: 176 cells 0·71 o/oo albumin and globulin test ±. No clinical improvement. Died.

Case 2. M. K.—C.S.F before treatment: 150 cells, 0·71 o/oo albumin, Weichbrodt reaction ++. After a first injection of 2 grammes tryparsamide the trypanosomes were still present in the blood and were considered to have a certain degree of arsenic-fastness. Therefore, the patient was treated with a considerable amount of Bayer 205 and the antimony compound tryatibine. From October 1939 to May 1940 he received a total of 20 grammes Bayer 205 and 20 grammes tryatibine.

The C.S.F was still altered (69 cells, 0·56 o/oo albumin) and the following courses of tryparsamide injections did not improve this or the clinical state of the patient. On 26th June 1941 lumbar puncture showed 506 cells 0·71 o/oo albumin and a very positive globulin test.

He was then injected with 5 × 0·05 *gramme* and 4 × 0·075 *gramme pentamidine* without clinical improvement, but the C.S.F was better: 184 cells, 0·56 o/oo albumin.

Treatment with tryparsamide Bayer 205 and antimony compounds was tried again but after 6 months the trypanosomes were still numerous in the altered cerebrospinal fluid.

Case 3. I. K.—On the date of diagnosis, the C.S.F contained 220 cells, 0·71 o/oo albumin, and excessive globulin. The trypanosomes did not seem tryparsamide-fast. But after 1½ years treatment with tryparsamide Bayer 205 and tryatibine there was only a slight improvement. Pentamidine was then tried, when the C.S.F still showed 59 cells, 0·4 o/oo albumin. The patient got 2 × 0·05 gramme, 1 × 0·06 gramme and 7 × 0·16 gramme partly intravenous, partly intramuscular. No changes in the clinical state nor in the C.S.F.

Case 4. F. E.—A similar case with 290 cells, 0·65 o/oo albumin in the cerebrospinal fluid. Treated for 1 year with tryparsamide tryatibine and Bayer 205. When treatment *of pentamidine was started, the analysis of C.S.F showed* 57 cells 0·56 o/oo albumin and a high positive globulin test. The patient received 1 0·06 gramme 7 × 0·1 gramme intravenous, and 2 × 0·1 gramme intramuscular.

No appreciable result: the C.S.F still contained 190 cells and 0·71 o/oo albumin.

Further treatment with tryparsamide Bayer 205 and antimony was equally useless. Died in September 1942.

Case 5. I. M. B.—The combined treatment of Bayer 205 tryparsamide antimony and pentamidine, has given a fairly good result in this advanced case a classical sleeping-sickness case with blood infection and altered C.S.F: 267 cells 0·65 o/oo albumin and Weichbrodt ++.

The patient was injected with 6 × 2 grammes tryparsamide 3 × 2 grammes Bayer 205 4 × 0·5 gramme tryatibine and pentamidine 1 × 0·05 gramme, 9 × 0·10 gramme. One month later the C.S.F showed 23 cells 0·32 o/oo albumin, Weichbrodt normal.

But 6 months later the C.S.F was nearly normal: six cells, 0·22 o/oo albumin, and the condition of the patient was good.

Case 6. Z. B.—Advanced case insane. C.S.F 170 cells, 0·4 o/oo albumin, Weichbrodt ++. The combined treatment started with 10 × 2 grammes tryparsamide and 7 × 0·5 gramme tryatibine. The C.S.F was then distinctly improved: 4 cells, 0·4 o/oo

albumin. The mental state was nearly normal. The patient then got 1 × 0·05 gramme pentamidine 1 × 0·1 gramme intravenous and 8 × 0·1 gramme intramuscular.

He appeared to be cured. The analysis of C.S.F. after 3 months: 3·2 cells, 0·22 o/oo albumin. After 9 months: 12 cells, 0·22 o/oo albumin, Weichbrodt negative.

II. Preventive Action of Pentamidine.

The above experiments suggested that the drug has a prolonged and cumulative action together with a slow rate of elimination or excretion. The process must be similar to that of Bayer 205 apparently forming some stable combination with proteins of the body and so maintaining the trypanocidal activity of the pentamidine over a long period.

A. EXPERIMENTS ON GUINEAPIGS.

1.—*One Single Dose and Infective G. palpalis.*

G.P. No. 251.—One single dose of 0·002 gramme per kg. on 19th May 1941. Infective tsetse flies were fed from 21st May to 29th July. On dissection five salivary gland positive flies were found. The animal was positive on 30th July and infected by the last batch of flies. The probable duration of protection including the incubation period was 72 days.

G.P. No. 29.—One single dose of 0·002 gramme per kg. on 13th June 1941. Infective flies were fed on the animal from July to 20th September. Eleven positive flies have been dissected in the four batches used for this experiment. The duration of the protection including incubation (average of 12 days) was 117 days.

Flies were fed every two or three days on the animals and the guineapigs were bitten by infective flies at least twice a week.

2.—*One Single Dose and Positive Blood.*

Three guineapigs protected with a single dose of 0·002 gramme per kg. were inoculated once a week with blood containing numerous trypanosomes. The strain was not drug fast. Protection lasted for 69 to 115 days, this interval including the incubation period.

Four more animals, two injected with 0·002 gramme, two others with 0·003 gramme per kg., were inoculated as above, but the strain of trypanosomes was strongly trypanamide-fast. One died negative on the 115th. The survivors were protected for 22 to 107 days.

3.—*Three Cumulative Doses of 0·002 Grammes at Short Intervals and Infective Flies.*

One of the animals which received three doses of 0·002 gramme per kg. in 5 days was exposed to infective bites during 10 months. Fourteen batches of flies have been used and flies were fed every 2 or 3 days. Only one batch did not contain any positive fly, but the remainder contained forty-six tsetses with heavy salivary gland infections. The guineapig became positive on the 327th day and thus had been protected for 315 days.

Another guineapig treated in the same way and bitten by 32 positive flies died on the 252nd day of the test, still negative. The protective period was thus about 240 days.

4.—*Three Cumulative Doses of 0·002 Gramme per Kg. at Short Intervals and Repeated Inoculation of Infected Blood.*

The guineapig was injected once every week with heavily infected blood from various strains. The protection given by the drug lasted 120 days (incubation period included).

B. EXPERIMENTS ON VOLUNTEERS.

Two natives submitted themselves to this experiment. Both had been free from sleeping-sickness and syphilis in the past and of any treatment that could influence the results.

Bonkumu received one single injection of 0·002 gramme per kg. on 9th August, 1941. From 11th August, 1941 to 8th August, 1942, batches of tsetse flies were fed on the volunteer every 2 or 3 days. All these batches contained at least one positive fly and the total amount of flies dissected and found infected in the salivary glands was sixty. The first trypanosomes appeared in the blood of Bonkumu in August, 1942, 1 year after the protective injection.

Moya was treated on the same dates. He got a single injection of 0·003 gramme per kg. Batches of flies were fed on him at the same rate, and he was stung by thirty-two tsetses infected in the salivary glands. This volunteer was first positive on 1st June 1942, 295 days after protective treatment.

Many precautions were taken during these experiments. Blood films were examined daily from the 1st week. One month after they were first bitten by infective glossinae blood cultures were made for the first time and cultures were then made every 10 days. A total of twenty-three blood cultures were made for Moya, and of thirty for Bonkumu. The method of blood cultivation was that described by Brutsaert and Henrard (1936).

As it seemed possible that trypanosomiasis might develop in these volunteers without blood infection but with a direct involvement of the central nervous system the C.S.F. of Bonkumu was examined on the 6th and the 10th month of the experiment. The C.S.F. remained normal.

The volunteer Moya was the first found infected on 1st June, 1942. A thick blood film stained with Giemsa was positive. The blood culture was soon after also positive in ten test tubes inoculated on 6th June, and found positive on 11th June. Laboratory-bred flies were fed on Moya from the first day of his positiveness. The cyclical transmission of his trypanosomes succeeded but infective flies were found only in the batches fed on him on the 2nd day. For this transmission nine batches were used containing a total of 417 flies. Amongst those flies, one had a gut-only infection on the 11th day, one gut-proventriculus infection the 42nd day. All those infected or infective flies were fed on 2nd June and it is interesting to note that from the 2nd to the 17th of June the thick films were negative as well as a blood culture made on 8th June. It may be mentioned that after 3rd June the best method of diagnosis, *i.e.*, xenodiagnosis and blood culture failed. The C.S.F. examined on 12th June was also normal.

The volunteer Bonkumu although protected by a smaller dose of only 0·002 gramme per kg. remained negative for a longer time, in fact for a whole year after the preventive injection. The trypanosomes were seen once in the thick film on 10th August but blood cultures on the same day as well as those made on 17th August and 22nd August, were still negative. In the same period, *i.e.* 11th to 21st August, 1942, the parasites disappeared from the blood, but were regularly present after this date. Although flagellates were present in the peripheral blood on 20th and 22nd August, the blood cultures on the same days did not succeed. Blood cultivation was not positive until

27th August, *i.e.*, 17 days after the first demonstration of trypanosomes in the thick film.

One cyclical transmission has also been tried on Bonkumu soon after evidence of his infection From 10th to 27th August nine batches of clean flies (*i.e.* 386 flies) were fed on the patient Infected flies were found only in the batches fed on 24th and 25th August, two gut-only infection on the 12th and 15th day six gut proventriculus-gland infections on the 18th 28th 30th 43rd and 44th day after the infecting meal It is noteworthy that no infection occurred in the flies fed when the patient's blood was negative on direct microscopical examination

From the clinical point of view, the first days of the illness in these volunteers showed a very peculiar picture. The scarcity of the trypanosomes the negative blood cultures and xenodiagnosis for a relatively long period demonstrate how difficult the early diagnosis would be in natives protected with pentamidine moreover the two patients had none of the symptoms observed in other volunteers and as a matter of fact, no symptoms at all Even when trypanosomes were readily found in the blood the temperature remained normal. At the spot where the flies have bitten a superficial and painful nodule is often seen this also was absent in our patients.

Bonkumu and Moya were treated and cured with strong doses of Bayer 205 It is doubtful how their illness would have turned out if left alone It must be remembered that natives protected by Bayer 205 prophylactic doses may show a cryptic or inapparent evolution of sleeping sickness Pentamidine has probably similar effects

III. Effect of Pentamidine on Infective Flies

Three infective glossinae have been isolated from batches of flies fed on an infected *Cercocebus galeritus agilis* As in former experiments the flies were separated each one in a box, and fed on guineapigs so that the animals gave evidence of the infective responsible fly

Fly 1.—Fed on a guineapig 32 hours after the animal had received 0·002 gramme per kg This meal did not disinfect the fly which was fed on five clean guineapigs at intervals of 3 days all of them became positive after an incubation period of 13 to 21 days. The fly was killed and dissected 19 days after the medicinal meal and found heavily infected in the gut and the salivary glands

Fly 2.—This experiment was similar to the previous one The result was the same.

Fly 3.—The guineapig used for the disinfecting meal received a larger dose of 0·003 gramme per kg of pentamidine. The fly was fed 48 hours after this injection. All clean guineapigs on which this fly was fed became positive. The fly was dissected and found infected in gut and glands more than one month after the pentamidine-blood meal.

This experiment being entirely unsuccessful, the effect was tried of feeding the flies on infected animals during the cyclical evolution of *T. gambiense*

Number of flies	Medicinal meal	Dose Grammes per kg	Number of infected Flies		
			Gut	Proventriculus	Glands
40	10th day	0·002	4	–	3
30	9th	0·002	1	2	18
22	12th	0·003	–	–	2
45	12th	0·003	–		1
45	9th	0·003	–	4	6
39	9th	0·003		–	–

The uninfected guinea-pigs bitten by these flies became positive. Control with batches of flies not fed on infected animals showed a comparable number of infected flies. The figures are the following —

Flies fed on treated animal	infected	28	per cent.
	gland infections	21	„ „
Flies fed on clean animal	infected	32·5	„ „
	gland infections	25·8	„ „

This slight difference does not indicate a real action of the drug on the cyclical evolution of the trypanosomes in the body of the glossina.

Discussion.

As far as the curative value of the drug and its toxicity is concerned our results may be compared with those obtained with animals or with patients by Lourie and Yorke (1939), Lourie (1942), Sicotrias (1941). There is however a difference in our appreciation of the curative activity in advanced cases. We consider that pentamidine does not reach the deep nervous lesion of the trypanosomiasis as is shown by the slight action on the alterations of the cerebrospinal fluid. Compared with say trypanamide the drug which really can clean an altered lumbar-fluid, pentamidine is disappointing. Even if there is an improvement in the cell count and the albumin and globulin rate, no cure can be claimed as long as normal figures are not obtained. Therefore pentamidine should be used only when the trypanosomes are arsenic-fast or when optic neuritis is to be feared, but without great hope of obtaining definite results.

In early cases pentamidine cures easily and safely *gambiense* sleeping sickness. It will replace Bayer 205 in arsenic-fast cases, when a first curative dose of trypanamide fails to sterilize the peripheral blood.

But it is as a preventive that pentamidine seems to have the greatest value. As happens with Bayer 205 the drug is eliminated slowly and accumulates in the body retaining a strong trypanocidal action which prevent infection by flies as well as by mechanical transmission.

At least in the case of volunteers the drug has a lasting prophylactic action probably stronger than that of Bayer 205 The useful prophylactic dose has no toxic effect, and as it appears that the drug is as effective when injected in the muscles as when injected in the veins a mass prophylaxis of the population could be carried out easily and in a short time A large scale trial of the product was started in 1942 in a heavily infected trypanosomiasis focus of the Kwango district in Belgian Congo and we hope to collect the first results at the end of this year *

Owing to the necessity of following practical lines in a mass drug prophylaxis, no attempt was made to try higher doses than 0·002 and 0·003 gramme per kg., nor repeated doses It must be borne in mind that the success of such prophylaxis depends on the swiftness and the speed of examinations, and a summoning of the whole population and the painless treatment without toxic after effects. We surmize that every 6 months all the injected natives have to be examined again and occasionally re-injected It is important to detect all the newcomers and to protect them as they may import new strains from the vicinity cryptic cases may occur and will be diagnosed only by some clinical symptoms confirmed by the alteration of the cerebrospinal fluid

It was of interest to know if pentamidine carried in the blood of protected natives would disinfect the glossinae or impair the cyclical development of the trypanosomes in flies which had fed on carriers of the disease. But it seems that the drug has no such action and we remember that in similar trials made with Bayer 205 we had to use large doses of this drug to obtain marked results.

Summary and Conclusions

1 Pentamidine (May and Baker 800) has a strong trypanocidal action on *T gambiense* This action is not impaired by the arsenic-fastness of the flagellates

2. The trypanocidal action of pentamidine has a slow start and lasts long Sterilization of the blood is only obtained at the 3rd day after the optimal dose of about 0·001 gramme per kg To avoid toxic effects doses of 0·002 gramme per kg and over must not be repeated more than twice a week. Repeated doses increase the curative action especially by accumulation of the drug in the body

3 In the case of sleeping-sickness patients intramuscular administration of the drug is less toxic and has the same effects as by the intravenous route The drug does not cure or improve advanced cases with marked involvement

* The first results, 3 months after the injection of pentamidine 0·002 to 0·003 gramme per kg are promising Not a single new case was found amongst the protected natives Among the natives used as controls 2 5 per cent. of new infections were discovered The experiment took place in a few villages with a total of more or less 500 inhabitants half of them being protected.

of the central nervous system. It is however useful in early cases, and is advocated when the trypanosome is resistant to other drugs, such as trypanamide or similar arsenical compounds.

4 Flies fed on animals injected with average doses of pentamidine are not disinfected of their trypanosomes, nor is the cyclical development of their trypanosome infection influenced.

5 Evidence is adduced of the prophylactic value of pentamidine Guinea-pigs are better protected by three doses of 0·002 gramme per kg and were free from infection for at least 120 days. Volunteers injected with a single dose of 0·002 or 0·003 gramme per kg resisted for 10 to 12 months repeated bites of infective tsetse flies.

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THE SICKLING PHENOMENON IN THE BLOOD OF WEST AFRICAN NATIVES

BY

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Since Herrick (1910) first pointed out the association of sickle-shaped erythrocytes with a severe anaemia, a considerable volume of literature has appeared, especially in recent years, on one or other feature of the sickling phenomenon. Most of this literature has emanated from the Western Hemisphere and is based on observations made on American negroes. This paper gives an account of investigations and observations which were carried out on West African natives, and mainly directed to a determination of the incidence of the sickle-cell trait.

Although the American negro population was originally derived from West Africa very few cases of sickle-cell anaemia have been reported from these colonies and no account of the incidence of the sickle-cell trait in West African natives can be found in the literature apart from the work of E. C. Smith (1934)

I wish to thank Lt. Col. J. C. Leedham-Green R.A.M.C. and Lt.-Col. W. M. MacNaught R.A.M.C. for much encouragement and for allowing me to refer to the patients and notes of the surgical and medical divisions.

I am grateful to Brig. R. A. Hepple, O.B.E. M.C. D.D.M.S. West Africa, and Brig. G. M. Findlay C.B.E., Consultant in Tropical Medicine West Africa Force, for their encouragement and interest in this communication.

The incidence of the sickle-cell trait was investigated in a group of nearly 600 men, constituting natives from the Gambia, the Gold Coast, Nigeria, and the Cameroons. They consisted of a large percentage of all hospital admissions during a period of over 6 months, together with a smaller group of fit soldiers employed on hospital and other duties. The incidence of the trait among the natives of one Gambian village the population of which was mainly derived from one family (*Bojang*), was also determined.

TECHNIQUE.

(*a*) *The Moist Preparation Method*.—A drop of capillary blood was placed on a clean dry slide and a coverslip was put over it. The edges were sealed immediately with vaseline and the preparation kept at room temperature and examined at intervals up to 36 hours.

(*b*) *The Test tube Method*.—This is a modification of the method described by Beck and Hertz (1935). Approximately 2 c.c. of venous blood was placed in a 3·8 per cent. citrate solution contained in a test tube 6 inches by ¾ inch under a layer of liquid paraffin. Formaldehyde, 10 per cent. solution in saline, was then added beneath the oil after 24 hours had elapsed. After allowing 30 minutes for cell fixation, moist preparations of the fixed cell suspensions were then examined.

(*c*) *The Small Test tube Method of Beck and Hertz* (1935).—A drop of blood from a finger was allowed to fall into a citrate solution in a Wassermann tube and a layer of liquid paraffin added. Formaldehyde was then used as in (*b*) to fix the cells after 24 hours. The fixed cell suspension was then examined.

Stains as a preliminary procedure were not employed in any of the above methods.

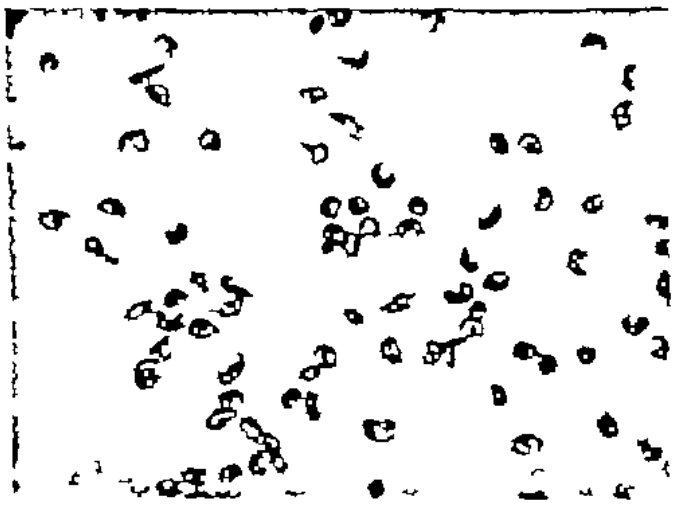
Tests for the sickle-cell trait were also made on "blood" obtained by sternal bone marrow puncture.

Although the test tube method (*c*) is described as a very delicate test, no significant difference in the results from those obtained when using methods (*a*) and (*b*) was found. The test tube method (*b*) was found particularly useful when cells fixed in the sickle form were required for demonstration or for permanent preparations.

Tests for sickling *in vivo* were made by collecting venous blood into a paraffined syringe and placing the blood immediately into 10 per cent. formol saline under liquid paraffin.

In a few instances the vital dye method of Hansen Pacas (1937) was used. An alcoholic solution of brilliant cresyl blue, a 1 per cent. solution in 85 per cent. alcohol, was spread on a clean dry slide and allowed to dry in a dust-free atmosphere. A drop of capillary blood was then placed on the slide and a coverslip put over it. The edges were immediately sealed with vaseline and the preparation examined at intervals up to 36 hours. It was interesting to find that the brilliant cresyl blue inhibited the formation of sickle-cells, an

effect first described by DIGGS and PETTIT (1940) In one case (90 per cent. of whose red blood cells were known to sickle within 15 minutes of preparation of a sealed moist blood specimen) who was retested using cresyl blue filmed slides, no sickling was found to have occurred after 6 hours and only 15 per cent. of the red cells had assumed the sickle form after 12 hours. This method was found useful in tracing the changes occurring in the erythrocytes during the process of sickling on account of the slowing down of the rate at which the cells assumed the sickle form HAHN and GILLESPIE (1927) studied the characteristics of sickle shaped erythrocytes, and like them it was found that at first the cells expand and assume a spheroidal form just as they do in the first stage of saline haemolysis Transformation into the multi-pointed sickle



CLASSICAL SICKLE-CELLS.
Formalin-fixed preparation

forms then occurs slowly In capillary blood preparations it was noted that the reticulocytes took a longer time to sickle than mature erythrocytes

GROUP I WEST AFRICAN SOLDIERS

In this group 561 soldiers were examined and 19·9 per cent. were found to have erythrocytes which sickled *in vitro* This group consisted of 362 natives from Nigeria and the Cameroons 18 75 per cent. of whom sickled 132 natives from the Gold Coast, 16·6 per cent. of whom sickled, and 67 natives from the Gambia 28 3 per cent. of whom possessed the sickle-cell trait.

It may therefore be assumed that 20 per cent. represents the incidence of the sickle-cell trait in a group of British West African male natives chosen at random This figure is nearly three times as high as that found by COOLEY and LEE in their examination of 400 American coloured patients 7 5 per cent. of whom were found to possess the sickle-cell trait. This figure obtained by COOLEY

and LEE for American negroes has been corroborated by JOSEPHS (1928) who obtained a result of 5 to 7 per cent., and other workers. The highest figure for any one group in this series was found among the Gambian natives (28·3 per cent.) and included six cases of sickle-cell anaemia, of which four died. It is realised that this high figure for Gambian soldiers may be due to the relatively small number examined and to the high rate of inbreeding

FINDLAY (personal communication) has recently examined a random group of 300 soldiers from the Gold Coast and found the incidence of sickling to be 15·5 per cent.

TABLE.

Number Examined.	Race.	Number Positive.	Positive Percentage
224	Nigerians	50	22·3
138	Cameroons	21	15·2
132	Gold Coast	22	16·6
67	Gambians	19	28·3
561	All Races	112	19·9 per cent.

GROUP II NATIVES OF A GAMBIAN VILLAGE.

A small group of sixty nine villagers of both sexes, mostly members of one large family (*Bojang*) was tested for the sickle-cell trait. The incidence of the trait in this group was found to be 18·8 per cent. Of these sixty-nine persons, forty six were males and twenty three were females Although the numbers are small, it is interesting to note that 22 per cent. of the males were found to be sickling and that the blood of only 13 per cent. of the females sickled *in vitro* One family representing the parental first and second filial generations respectively and comprising twenty-two members, was included in this group Males contributed twelve and females ten members respectively Blood from five males (42 per cent.) sickled only one of the ten females showed evidence of the trait. Remembering that the trait has been shown to be inherited as a Mendelian dominant character (HUCK 1923) it is worth while pointing out that only 15 per cent of the remaining forty-seven members were found to sickle.

Full blood counts were carried out on a number of the soldiers in Group I The mean red cell count for those whose blood sickled *in vitro* (excluding those patients who were thought to be cases of sickle-cell anaemia) was found to be 4 100 000 red cells per c.mm In the non-sickling class of patients a mean red cell count of 4,250 000 cells per c.mm. was recorded. Cases of nutritional anaemia, hookworm anaemia, and anaemia due to other causes were included in both the sickling and non sickling classes.

The 561 members of Group I may be subdivided into fit soldiers (302) and those suffering from acute or chronic disease (259) and for the purpose of this investigation patients admitted into hospital on account of injuries and gonorrhoea have been included among the fit soldiers. In the class of fit soldiers the incidence of sickling was 15 5 per cent., whereas among those suffering from various diseases the incidence was 25 per cent. A further analysis of the latter subgroup revealed that the highest incidence of sickling was in a series of forty-six patients admitted with respiratory diseases (lobar pneumonia, broncho-pneumonia, pulmonary tuberculosis, pleurisy and lung abscess) In this series the incidence of sickling was 28 3 per cent. No significant variation from the figure of 25 per cent. was found for any other group of diseases.

Summary

1 The incidence of the sickling trait in the natives of British West Africa has been examined.

2 The figures of 15 5 per cent. for fit males and 25 per cent. for males suffering from acute and chronic diseases were found.

3 This incidence is considerably higher than previous estimates for American negroes The reasons for this are suggested

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ORDINARY MEETING
of the Society held at
Manson House, 26, Portland Place, London, W ,
on
Thursday, 20th January, 1944, at 8 p.m
THE PRESIDENT
SIR HAROLD SCOTT K.C.M.G , M.D F.R.C.P
in the Chair

PAPER

IMPORTANT DISEASES AFFECTING WEST AFRICAN NATIVE TROOPS

BY
R M MURRAY LYON M.D F.R.C.P MAJOR R.A.M.C.

I propose to review the more important diseases seen in the African medical wards of a general hospital in the Gambia. I did not bring back with me the actual figures for admissions so no statistics will be given but *only* a rough general survey The patients were all African soldiers of the R.W.A.F F and were drawn from all parts of the Coast from the Cameroons to the Gambia.

A considerable difference in the incidence of various diseases was found according to the colony of origin.

In the first place we were surprised to find such a high proportion of the patients were admitted for non-tropical respiratory diseases. Lt.-Col. MACNAUGHT and I have published in the *British Medical Journal* our findings on the incidence of chest complaints which accounted for almost a third of all medical admissions. The chief features of the pneumonia cases were the dramatic response to sulphapyridine, the low death-rate and the low complication rate. The other important non-tropical conditions were outbreaks of chickenpox, cerebrospinal fever and vaccinia.

CHICKENPOX

The majority of the cases of chickenpox were mild but there were a number of very severe cases in which the men were acutely ill. In these patients the distribution of the rash was more that of smallpox, with maximum lesions on the face and periphery of the limbs. In all cases, however typical chicken pox lesions were always present on the trunk. The main importance of these outbreaks of chickenpox lay in the attacking of patients already under treatment for trypanosomiasis. These patients invariably showed a very marked deterioration in their condition, shown both clinically and by an increased cell count and protein content of the C.S.F. This resulted in longer hospitalization and, in some, eventual medical boarding out of the Army.

CEREBROSPINAL FEVER.

Fulminating attacks were common, so that soldiers apparently in their usual health would collapse on duty and be unconscious on arrival at hospital in a matter of an hour or two. Quite a number were found dead or moribund in their huts or tents. The vast majority of these cases responded dramatically to intravenous sulphapyridine although often their condition appeared desperate. Those that died were found on postmortem examination to have an acute encephalitis in addition to meningeal infection, but suprarenal involvement was not seen. A great many of these men at no time showed typical clinical signs and neck rigidity and Kernig's sign were often absent. This was so common that a routine lumbar puncture was performed on all acutely ill patients not showing definite localizing signs and in this way a number of cases were diagnosed that might have been missed until too late.

In all cases, fulminating or not, a rash was very rarely seen—at the most a few scattered purpuric spots. The routine treatment of cases not too severely ill to swallow was the oral administration of sulphapyridine in suspension. Two gramme doses for the first twice and then 1 gramme 4-hourly. The more severe comatose or semi-comatose cases were given intravenous sulphapyridine in doses of 1 gramme until able to swallow. No toxic effects from

sulphapyridine were met with amongst any of the patients No sequelae were noted apart from one case which showed a relapse This man had apparently recovered and after a few days of normal temperature again complained of headache, stiffness of neck and showed a rise in temperature and pulse-rate Lumbar puncture revealed a turbid fluid and meningococci were isolated. The organisms were not sulphapyridine resistant and a second course cleared up the condition completely

VACCINIA.

Several dozen Cameroons troops had to be admitted to hospital following vaccination against smallpox. In addition to general malaise, pyrexia and local inflammation all these men showed joint involvement. The majority had pain redness swelling and limitation of movement affecting one knee. A few had involvement of an elbow or wrist In all cases the condition cleared up completely in a few days with symptomatic treatment. This response to vaccination did not appear to be related in any way to a higher incidence in these men of yaws or sickle-cell disease.

Tropical Diseases

The vast majority of African soldiers were found on admission to hospital to have several tropical infections and it was sometimes difficult to decide which was the actual cause of his reporting sick. A soldier might for example, be admitted complaining of oedema, dyspnoea, weakness of the legs and on examination show obvious foot yaws onchocerciasis and a moderately heavy hookworm infestation The actual cause of his major disability might however be vitamin B complex deficiency On intensive treatment with marmite, the symptoms would clear up and not all the other conditions might require treatment at all Helminth infections being practically universal had to be ignored unless the infestation was heavy and giving rise to very definite signs and symptoms. The two main weak points in the West African appear to be the lungs and liver The importance of chest trouble as a cause of hospitalization has already been mentioned. It was our experience that it was unusual to find a normal healthy liver at autopsy no matter from what the man had died. The majority showed some evidence of early cirrhosis even though they were under 30 years of age and in a few cases the disease had progressed to portal obstruction The only form of neoplasm seen in the medical wards was primary carcinoma of the liver In two or three cases after only a few weeks of ill health the man would die with enormous new growths in the liver which also showed portal cirrhosis.

This prevalence of liver disease made *toxic hepatitis* following therapy with arsenicals and anthelmintics very common All patients given drugs liable to affect the liver had to be very carefully watched and were always put

on to extra glucose. Jaundice was so frequent after carbon tetrachloride that the administration of this drug for the treatment of ankylostomiasis was discontinued. One otherwise apparently healthy young adult with ankylostomiasis of moderate severity died of liver necrosis following the administration of the standard treatment —

Carbon tetrachlor	2 c.c
Ol. chenopodium	1 c.c
Paraffin liq	30 c.c.

At postmortem he was found to have had well advanced portal cirrhosis with little liver reserve and there was acute necrosis of the remaining liver tissue.

In the European wards of the hospital *infective hepatitis* was common and similar cases occurred amongst the African patients. A diagnosis of infective hepatitis was only made in these cases, however when other conditions had been excluded (such as toxic hepatitis or amoebic hepatitis). On the whole this disease was more severe in the African and ran a longer course with a more marked icterus, and this was presumably due to their having less liver reserve. Treatment was by low fat/high carbohydrate diet as far as possible. Dieting was always very difficult as it was practically impossible to make the patients understand the importance of only taking the food given. Unless carefully watched the men would always take extra food cooked in the usual palm oil or ground nut oil stew

Amoebic abscess was only diagnosed once but *amoebic hepatitis* was common. The usual signs and symptoms were low or moderate fever with some leucocytosis, and complaint of vague upper abdominal pain and indigestion. The liver was usually palpable and tender and a slight icterus was common. Occasionally well marked jaundice was seen In many instances no definite history of previous dysenteric symptoms was obtained from the men. This was often doubtless due to language difficulties when dealing with men enlisted from bush villages where only a local dialect was spoken. On repeated examination of the stools, cysts or active trophozoites of *Entamoeba histolytica* were found in about half the cases before treatment was started. In the others positive findings were obtained after some days' treatment with a daily dose of 1 grain emetine H Cl. All the patients responded satisfactorily to a course of 10 grains of emetine hydrochlor with settling of temperature and clearing up of symptoms. In some, however cysts were still present in the stools and they were given a 7-days course of E.B.I and stovarsol, getting the full course given to African patients admitted with frank amoebic dysentery Treatment with retention of enemata of quinoxyl was not found practicable in the African wards.

Trypanosomiasis

Trypanosomiasis being endemic in the Gambia, the disease was commonly seen in the troops enlisted in the colony Cases were also seen amongst men

from the Gold Coast who had come from a sleeping sickness district, and there were other cases of men apparently infected after reaching the colony, as also occurred with a few Europeans

Symptoms and Signs In no case was a patient seen showing the local changes at the site of the bite nor was such a history obtained. The men were either admitted on account of the posterior cervical glands being enlarged with or without discomfort or on account of increasing lethargy either physical or mental, and complaint of persistent headache. Often the soldiers had not reported sick but were referred to the R.M.O. by the B.N.C.O. in charge, who had noticed a falling off in the man's military efficiency. Sometimes the true state of affairs was only discovered after a man had been up on charges of laziness or insubordination. The early diagnosis of the disease, which was insidious, depended chiefly on the alertness of the Europeans, including the R.M.O. of the man's unit. An intelligent African orderly would often spot the change in the man's mentality when a European only thought he was having one of the dumb spells which the best of the Africans are prone to show at intervals.

The finding of trypanosomes in the peripheral blood was the exception rather than the rule and diagnosis chiefly depended on gland puncture and examination of the cerebrospinal fluid. About half the cases had nervous system involvement with cells in the C.S.F. increased from 30 to 1,000 per c.mm., a positive globulin, and the total protein content increased from 30 up to 80 mg. per cent. The glands in most cases were soft and elastic but in the more advanced cases the glands had reached the hard fibrous stage. In the Gambia congenital bilateral ptosis was not uncommonly seen, and this gave rise to a mistaken spot diagnosis of trypanosomiasis on more than one occasion. Pyrexia was not a marked feature and no typical temperature was recognized though an irregular low fever was not uncommon. Dryness of the skin which had lost its healthy shiny appearance was seen in the more advanced cases and a few showed a transient oedema about the eyes and face. The more advanced cases might even show a masklike appearance similar to that of Parkinsonism. Cases of glandular fever were found in the European wards and often the glandular enlargement found in the Africans without any other very definite signs or symptoms was similar. The absence of typical blood changes and the finding of trypanosomes on glandular puncture, however, made the diagnosis quite clear. The Paul Bunnell agglutination test was not found helpful as negative results were found in apparently definite cases of infective mono-nucleosis. Whether this was due to some error in technique when preparing the sheep cells or to its being a different virus infection we could not decide.

The technique we found most satisfactory for gland puncture was as follows —

After cleaning the skin with spirit the chosen gland was firmly anchored between the left thumb and forefinger and a perfectly dry needle was pushed

into the gland and poked around. After withdrawal the needle was engaged to a dry syringe whose plunger was half drawn back and the contents of the needle squirted carefully on to a slide. After removal of the small plug of black skin the cover slip was put on and the slide examined Failure to remove the plug of skin gave too thick a film for satisfactory examination. Before starting treatment all the patients had a C.S F examination and were fully investigated by the ophthalmic specialist. The routine course of treatment consisted of intravenous injections every 5 days, starting with four doses of antrypol 1 gramme and continuing with 2 gramme doses of tryparsamide The total dosage of tryparsamide depended on the cell count and protein content of the C.S F which was checked at intervals The patient was also re-examined regularly by the ophthalmologist during treatment. No toxic effects from tryparsamide were noted with doses up to a total of 24 grammes. In many cases visual acuity was apparently improved but this was probably due to the patients becoming more co-operative as the lethargy wore off I have had no personal experience of treatment with pentamadine (M & B. 800) which was giving very alarming reactions owing to its effect on blood pressure

The results of treatment depended on how early the disease was diagnosed and treatment started. Cases with only lymphatic or early nervous system involvement were made fit to return to duty but more advanced cases with high C S F cell counts either did not respond sufficiently or relapsed later and had to be medically boarded. The majority of African soldiers were not tradesmen and were therefore not employable unless absolutely physically fit Patients fit to be returned to their units were kept under special observation there and sent back to hospital for review and repeat examination of their C S F after some weeks.

TROPICAL MYOSITIS.

There were always one or two cases of tropical myositis in the medical wards. This condition was chiefly seen in the natives of the Cameroons or the Eastern provinces of Nigeria The men were admitted to hospital with a complaint of pain and swelling in muscles usually of about 1/52 duration. The commonest situations were in the muscles of the limbs but the chest and abdominal wall muscles were also affected on occasion Usually there was only one lesion but sometimes a man would be admitted with two, or a second lesion would develop whilst in hospital. Apart from this disability the men appeared to be in reasonably good general condition and no causal factor or relationship with such conditions as filariasis, helminthiasis, or sickle-cell trait could be discovered. These cases were investigated surgically and histologically by Lt.-Col. LEEDHAM GREEN and Major EVANS, and the condition was considered to be an acute degenerative condition similar to Zenker's degeneration which might go as far as suppuration (pyomyositis) when staphylococcal bacteriaemia supervened

The clinical features were moderate pyrexia and a tender diffuse or circumscribed swelling in muscles, which might show marked heat and even fluctuation. Treatment consisted in rest, by splinting if necessary and the administration of analgesics as required. About half the cases were given a course of either sulphapyridine or sulphathiazole, but their progress did not differ materially from that of those left without chemotherapy Too early surgical interference had to be avoided as even cases apparently showing abscess formation might subside satisfactorily If however the temperature began to swing and a well-marked leucocytosis developed, surgical drainage was required. The usual period of hospitalization for those cases resolving spontaneously was about 3 weeks and longer for those requiring drainage. One fatal case was seen with extensive abscess formation deep to the pectoral muscles from which many pints of pus were evacuated. This man was in very poor general condition when first seen and died of bronchopneumonia in spite of energetic treatment.

VITAMIN B COMPLEX DEFICIENCY

Patients were admitted to hospital showing signs and symptoms indicative of varying degrees of deficiency of the vitamin B complex. Deficiency disease was most often seen in new recruits enlisted from up-country bush villages and was not often seen amongst soldiers on army rations.

In some cases the cardiovascular system was chiefly affected, whilst in others nervous system lesions were more prominent and skin and tongue might also be involved. Many complained of anorexia and flatulent dyspepsia.

Usually cardiac symptoms were the most prominent and the men were admitted to hospital on account of dyspnoea weakness and oedema On examination there might only be oedema of the ankles or all stages up to generalized water logging Often the patient's appearance would suggest nephritis but albuminuria was absent or only slight. The pulse was of low tension and there was tachycardia with marked cardiac dilation. The heart sounds tended to be evenly spaced and accentuated with reduplication and systolic murmurs. The nervous system lesions usually seen were reduced or absent deep reflexes, hyperaesthesia of calf muscles and dulling of sensation over the shins These patients often showed a positive squatting test, being unable to arise from the squatting position without assistance The other evidences of vitamin deficiency looked for included angular stomatitis, thickening of the scrotal skin crazy pavement appearance of the skin of the dorsum of foot and front of lower leg and atrophic glossitis.

Treatment in all cases consisted of strict rest in bed adequate diet and large doses of marmite. It was not found necessary to administer pure vitamins in the form of thiamin nicotinic acid or riboflavin The accompanying anaemia was treated by large doses of iron and when necessary hookworm infestation or other infection was treated during convalescence.

SICKLE-CELL DISEASE.

Many hundreds of cases were tested by Major R. W Evans for sickling and the sickle-cell trait was found in 20 per cent. by means of sealed blood preparations from a finger prick. In only a few instances, however had the men any symptoms or disability In cases with suggestive symptoms or signs, sickling *in vivo* in the venous blood was always looked for as well by the formol saline method under liquid paraffin. We did not find gross anaemia to be a common occurrence and in those showing anaemia there were always other factors present such as hookworm disease, chronic malaria, yaws, or nutritional deficiencies. We agree with Wintrobe that the term sickle-cell disease is preferable to sickle-cell anaemia as serious and even fatal complications may be present without the anaemia being pronounced. We saw cases with symptoms due to the thrombosis secondary to sickling suggesting acute osteomyelitis, perforated peptic ulcer various cerebral lesions with pareses. Treatment was purely symptomatic and several at postmortem showed evidence of previous thrombosis with old infarcts in brain, spleen and bowel. The majority of cases when first seen had already reached the stage of small atrophied spleen. One man, however with severe anaemia and haemolytic crises was considered suitable for splenectomy The treatment was highly successful so far as the anaemia was concerned but gave rise to an unexpected complication. Following operation, he had extremely severe attacks of malignant tertian malaria requiring the administration of intravenous quinine and the continuation of suppressive mepacrine indefinitely as in the European. During his malarial attacks blood smears showed the presence in the peripheral blood of malignant tertian parasites in all stages of development as is usually seen just prior to death in an overwhelming attack of cerebral malaria.

Sickle-cell disease must always be borne in mind in differential diagnosis in Africans showing indefinite cerebral symptoms, rheumatism-like pains in bones and joints, severe abdominal pain or leg ulceration. Yaws must always be first excluded. Treatment is usually not very satisfactory but correct diagnosis will prevent unnecessary operations being attempted.

MALARIA.

Being in a hyperendemic malignant tertian malaria area there was practically 100 per cent. infection of the Europeans, but the Africans had very little sickness due to malaria. It was noticed, however that on moving from one colony to another a certain proportion were admitted to hospital with an acute malarial attack. When the Africans went down with malaria they usually had a rigor temperature up to 103° or more and complained of severe headache. With profuse sweating temperature came to normal within 12 hours and the men were symptom-free. With these attacks parasites were usually found in large numbers in blood smears It was usual to give a 3 days course of treatment

only and return the men to duty In many cases the patients symptoms had subsided completely under mist. A.P C before the result of the blood film had been reported.

Over a period of 1 year only two cases of chronic malarial splenomegaly with anaemia were seen. These responded to treatment with adrenaline and quinine followed by large doses of iron No case of blackwater fever was seen in an African.

DYSENTERY

Second only to respiratory infections in number were the admissions for dysentery Approximately twice as many cases had bacillary dysentery as had amoebic. None of the bacillary dysentery cases were dangerously ill and only one case of Shiga was seen

The majority of the men were treated by sodium sulphate alone and only the more severe cases were given sulphapyridine sulphaguanidine or succinylsulphthiazole. Only one case out of several hundred was complicated. He developed multiple arthritis which took a long time to clear up Quite a large number of the cases of acute bacillary dysentery were found to be carriers of amoebic cysts, and required further treatment after recovery from their acute infection. Amoebic dysentery was treated by ten daily injections of 1 grain emetine hydrochloride followed by 3 grains E.B I and 8 grains stovarsol daily for 1 week. The men did not complain of symptoms referable to these drugs as did Europeans under similar treatment and there was often difficulty in keeping the men confined to the ward quite apart from being kept in bed. It was found quite impossible to treat Africans by means of quinoxyl retention enemata as sufficient staff was not available to keep the men in bed to retain the drug One fatal case was seen in a man who had very extensive chronic lesions affecting the entire colon. Quite a number of cases of ciliate dysentery were seen due to infestation with *Balantidium coli* These cases cleared up satisfactorily when treated by sod sulph. in the routine way used for the less severe bacillary infections

HELMINTHIASIS

As has already been mentioned minor hookworm infestation was common but only small numbers of cases were admitted primarily for this condition There were, however three men admitted with gross anaemia and circulatory failure whose haemoglobin had fallen to below 20 per cent. and who walked into the hospital in this condition One was given a preliminary blood transfusion and all three intensive iron therapy before the use of anthelmintics After the use of carbon tetrachloride had been discontinued they were given oil of chenopodium only in the absence of tetrachlorethylene. Round worms and tapeworms were quite often found and successfully evacuated after starvation and administration of santonin or ext. filicis. The tapeworms were invari-

ably *Taenia saginata* and almost always the worm came away in its entirety complete with head.

YAWS.

Yaws was naturally one of the major causes of disability amongst the African troops and large numbers had bone and joint or skin lesions. In some the yaws was the cause of admission to hospital whilst in many others yaws lesions sufficiently severe to require energetic treatment were incidental to other complaints. A special ward on the surgical side was opened for these soldiers and treatment with N.A.B or sobita was started. Many then could be discharged and continue treatment as out patients.

MURINE TYPHUS.

The last disease sufficiently serious and common to warrant mention is murine typhus, of which there were usually one or two cases in hospital either in the African or more rarely in the European wards. In the African patient a rash was not typically seen and diagnosis depended on a rising titre of the Weil Felix agglutination test. This rise in titre continued after the patients temperatures had settled and convalescence was well established. The main symptoms were headache pain in the back, marked increasing lassitude and anorexia. Some had well marked diarrhoea and enteric fever was suspected, but with the rising titre of OX 19 there was no increasing rise in the Widal which was variable in protected individuals. The pulse-rate also was higher than would be expected in typhoid. The treatment was symptomatic and though some were seriously ill all recovered with a return to normal temperature by lysis usually after 10 days sustained temperature of about 102° F

Discussion

Dr G Carmichael Low Major Murray Lyon in his very interesting paper does not mention syphilis or leprosy among the natives he had to deal with. In the old days in Uganda syphilis amongst the natives was very common —so much so that a special commission was sent out to investigate it some time after I had returned to England. There is no doubt that the African native is often a pathological museum. When doing autopsies on sleeping-sickness cases in Uganda one usually found evidence of old malaria (enlarged and pigmented spleens) dysenteric ulcerations, three or more helminthic infections, including intestinal bilharzial disease, and the different blood filariae. Major Murray Lyon does not mention filariae, but of course under war conditions it would not be practicable to make extended observations upon these.

Dr O. C Chesterman My experience of African natives was before the introduction of the sulphonamides, but in 16 years I never discovered an

empyema, although the mortality from pneumonia was very high One frequently saw septicaemic cases and meningeal infections but never an empyema

I am interested in the statement that cases of trypanosomiasis deteriorate when they have an intercurrent attack of chickenpox. One wonders whether the virus of varicella had anything to do with the breaking down of the barriers allowing the trypanosomes to get through to the central nervous system.

Were there any cases of bilharziasis, and were the cases of carcinoma of the liver in any way related to this condition ?

Sir Philip Manson-Bahr said the subject of sickle-cell disease was one to which considerable attention had been drawn in the United States, and comparatively few cases had been described in West Africa.*

The main pathological lesions appeared to be the fibrosis of the spleen and changes in the liver but the occurrence of cerebral thrombosis would appear to be new

Another point of importance in comparative medicine is the tolerance of different races to different diseases and drugs Major MURRAY-LYON mentioned contra indications for the use of carbon tetrachloride in Africans. Though he had given much of this to Europeans and Indians he had never had any serious concern about its effects on the liver The native has two weak spots —the lung and the liver and one must respect these in prescribing treatment.

The other point which arouses interest is the finding of jaundice in association with amoebic hepatitis. He had only seen two instances of this in his life and on both occasions there was a suspicion that it was combined with infective hepatitis but jaundice in association with amoebic abscess of the liver appears to be very exceptional.

The other point on which he would like to comment was gland puncture According to Kirk's method, this is the most useful procedure and can be applied to infections other than trypanosomiasis and leishmaniasis It could also be used for demonstration of *Spirochaeta pallidum* in the lymphadenitis associated with syphilis.

He considered that the present emergency was most suitable for general papers such as this.

Dr R Brunel Hawes I have been much interested in hearing Major MURRAY-LYON on our conditions in the Gambia for they resemble in some ways conditions in the East.

Carbon tetrachloride appears to be definitely dangerous to people whose diet is poor in calcium and first-class protein. I used to prohibit the use of this drug for these patients The poor high-caste Hindu who was not taking milk was an example.

* *vide* SMITH E C. (1934) *Trans R. Soc trop Med Hyg* **28** 209

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Dr C. C. Chesterman My experience of African natives was before the introduction of the sulphonamides, but in 18 years I never discovered an

for 2 days and then collapsing on deck. On admission he was delirious had a red-cell count of 800 000 per c.mm. and 80 per cent. of his red cells showed sickling within 2 hours He did extraordinarily well on transfusions of whole blood and was discharged, well, after about a month in hospital.

In contradistinction to the routine mentioned by Major MURRAY LYON we treated practically every African in patient for worms The great majority were infested with hookworm round worm tapeworm or whip worm —some had every variety—and it was my routine to carry out a de worming with oil of chenopodium a few days before the case was due to leave hospital This treatment would probably not remove all the worms, but certainly great numbers were evacuated

I was most interested to read in a private letter which reached me a few days ago sent from another military hospital on the Coast that they had two cases of blackwater fever in Africans in the hospital Blackwater fever as you will agree, is exceedingly rare in Africans and I wonder if we by treating malaria in the Africans with anti malarial drugs are not breaking down their immunity in some way I have always believed, and probably always will believe, that quinine, or its allied drugs has something to do with the production of blackwater and it will be most interesting to see if this disease increases among the African troops, thanks to our treatment of his malaria.

Finally I should like to mention how useful the sigmoidoscope was in the diagnosis of dysentery and *S mansoni* infection On many occasions when the laboratory findings were negative—and there was often a double check both the pathologist and myself examining different specimens of mucus—the case was referred to our surgeon who was an enthusiast with the sigmoidoscope and an expert diagnostician of what he saw He took a rectal swab from any affected area that he saw for further laboratory examination but his own provisional diagnosis was to be relied upon in the vast majority of the cases which he examined. I know he has a great number of records of these cases and I hope he may publish his findings in the near future.

Lieut.-Colonel Bomford I would like to congratulate Major MURRAY-LYON on the thorough review he has given us I served on the Gold Coast for a year and have one or two points to raise regarding diseases in Africans in that colony On one occasion we had an admission of several hundred soldiers returning from East Africa, mostly with respiratory infections mumps and chickenpox Chickenpox was very severe and in some cases difficulty was experienced in differentiating it from yaws We were told that chickenpox could last for some weeks, but in cases where the skin eruptions persisted our pathologist was usually able to demonstrate spirochaetes The lesions soon cleared up with a few doses of N.A.B Yaws of the feet was rather exaggerated and many cases of fissuring of the feet due to other causes were sent to hospital as yaws.

Our cases of cerebrospinal fever responded well to sulphapyridine. We made a suspension of broken-up tablets with gum acacia for intramuscular use and this was effective though painful.

We also had an interesting outbreak of heat exhaustion. A unit that was used to marching 30 miles a day in East Africa, returned to the West Coast, where after marching some miles through low lying plains, on a day when the humidity was high some 200 Africans and a number of Europeans fell out on the line of march. In all fourteen Africans were admitted to hospital four of whom were very ill and two died. The remainder responded well to saline infusion. In most cases dramatic improvement was noted after 100 or 200 c.c. had been given intravenously.

Another disease we saw in Africans was psychoneurosis, a common symptom of which was paralysis of the right arm. It was of the hysterical type and no treatment in hospital had any effect. In some cases this condition appeared to be due to a *juju*, and the patient assured us that he could be cured if he were allowed to return to his own village for appropriate native treatment. Of more interest was effort syndrome amongst West African personnel. Twelve typical cases of effort syndrome, almost all in semi-educated Africans who had seen service in East Africa, were discovered and studied by Major D. L. H. Gorman, who is, I believe going to publish a paper on this subject. We had a number of patients with psychosis.

Another very common disease in the Gold Coast is guinea worm infestation. These cases were all dealt with by the surgeons who found that twisting them out on a match stick was still the best form of treatment.

For bilharziasis of the bladder we used stibophen in preference to other forms of treatment.

Dr A. Felix asked if cases of one of the enteric fevers, especially para typhoid A fever occurred among the local population in the area, while the troops, who presumably had been inoculated against T.A.B. remained free from these infections. He also asked if Major Murray Lyon could give more information about his cases of murine typhus, especially how early in the disease a significant agglutination reaction with *Proteus* OX 19 had been obtained.

The President (Sir Harold Scott). Dr Stanton has already asked one question I had in mind. Were some of these patients with severe chickenpox described by Major Murray Lyon cases of alastrim? The two conditions are easily confused.

Speaking of cerebrospinal fever one of the most acute cases of cerebrospinal fever that occurred in my experience was during the last war. An officer was returning home from the mess, reeling from one side of the path to the other when two sergeants, thinking he was drunk, offered to take him back. To them he said, "I am not drunk, but very ill." He was taken to

hospital, where he died within 36 hours Were the meningococci typed in Major MURRAY LYON s cases ? I know of two men both carriers of different types of meningococci, who were segregated together and in time infected each other They each developed cerebrospinal fever caused by the type harboured by the other

Did any of the cases of infective hepatitis referred to follow yellow fever inoculation ?

I saw a great deal of tropical myositis when I was a young man and even wrote a paper on that subject. None of these cases was streptococcal in origin. There was at times very great enlargement of the muscles and rarely did they clear up without operation.

Major Murray-Lyon (in reply) Syphilis was hardly seen at all. The other venereal diseases were common and every African soldier had gonorrhoea at least once a year Syphilis was very rarely diagnosed.

We did not see many patients with leprosy because the vast majority of our men had been enlisted a very short time ago

I saw a few patients with bilharzial disease. There were one or two cases of *S mansoni* infection and slightly more of the other type It was not common amongst troops and we had to deal with no more than one case in hospital at a time. We treated bilharziasis with stibophen.

Major EVANS has brought back a mass of material on sickle-cell disease I understand that he is preparing a paper on this subject.*

Jaundice was quite definitely seen in Africans with amoebic infection of the liver I would not like to say that it was the effect of the amoebic infection but the jaundice cleared up whilst the patient was having the usual treatment with emetine I think the jaundice on the whole cleared up faster than ordinary infective hepatitis jaundice.

Amongst the population in the Gambia there were quite extensive outbreaks of alastrim going on with deaths among children The cases described looked far more like severe chickenpox, though one or two of them might have been some other condition and not chickenpox

I was interested to hear of the high incidence of enlarged spleens recently found in West Africans in the Gambia I had occasion, as a part time hobby to examine civilians of the local population and a very large proportion of the children had definite splenic enlargement. I found 50 per cent. of the children had grossly enlarged spleens and about 20 per cent. amongst adults

We also had a certain number of cases of worm infection which were often taken for cases of amoebic dysentery and in which the pathologist failed to find any amoebae or cysts. Guinea worm was frequently seen and was treated by the surgeons.

* EVANS, R. WINSTON (1944) Sickling phenomenon in the blood of West African natives *Trans R. Soc. trop Med. Hyg* 37 4 281

No cases of enteric fever were seen in Europeans or Africans. In the cases of murine typhus the rising titre of *B proteus* OX 19 occurred late in some cases as late as the 21st and up to the 30th day The rise of titre varied from 1:200 to 1 1 000

We had many cases of infective hepatitis in Europeans within 3 months of yellow fever inoculation. This followed inoculation with two batches used in this country (October 1942, and again December 1942)

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COMMUNICATIONS

PIGMENT METABOLISM AND RENAL FAILURE IN ACUTE SULPHONAMIDE HAEMOLYSIS RESEMBLING BLACKWATER FEVER.

BY

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AND

ATHENA KONDI
From the Wellcome Trust Research Laboratories

Introduction

The various intravascular haemolyses will broadly resemble one another in their blood pigment metabolism and other blood changes This has in fact, been found to be the case in such conditions as blackwater fever incompatible transfusions haemolytic jaundice and haemolysis from various drugs The extent and duration of the haemolytic process will obviously affect the amount and types of pigments found, as well as the other blood changes

Numerous reports have appeared during the past few years describing acute haemolysis following the exhibition of different sulphonamides Some of these reports have dealt with cases in which it was impossible to say whether there was actually any intravascular haemolysis or not, the authors merely describing dark urine no blood counts or spectroscopic examinations of the plasma or urine having been made. In other cases it seems that haematuria is being confused with haemoglobinuria. Disregarding these uncertain cases there are, however a number of undoubted examples of acute massive haemolysis accompanied by haemoglobinaemia and haemoglobinuria following the administration of sulphonamides and accompanied by profound falls in the red cell counts (Harvey and Janeway 1937 Kohn 1937 Wood 1938 Strasser and Singer, 1939 Keefer 1939 Tavat and Shepard 1939 Gilligan and Kapnick, 1941 Quick and Lord 1941

* Our thanks are due to the Director General of Medical Services (S.A.) for permission to publish this case and to Dr Joseph Gillman of the Witwatersrand University for the histological examination and report.

In the case outlined below complete quantitative pigment estimations in blood and urine were made, and correlated with other blood findings, so that a comparison between the pigment metabolism in this condition, blackwater fever and the other intravascular haemolyses was possible, bringing out the resemblances and differences between them.

As will be seen from the findings, there was a typical acute intravascular haemolysis, accompanied by methaemalbuminaemia, haemobilirubinaemia, and intracorpuscular methaemoglobinaemia and fall in the red cell count. Terminally the patient became anuric and azotemic, died, and a postmortem was done.

Case Report and Postmortem Findings.

On 16th February 1943 a European male was admitted to hospital suffering from an eczematous dermatitis of the arm, which, after admission, developed into a cellulitis. He was given 15 grammes of benzyl-sulphanilamide (M. & B. 125) over a period of 3 days.

18th February.—After receiving 12 grammes a slight icteric tint of his conjunctivae was noted.

19th February.—A further 3 grammes were given after which the patient passed a quantity of dark coloured urine.

20th February.—The sulphanilamide was discontinued as the patient became extremely ill, deeply jaundiced and complained of pain and exhibited tenderness in both loins and in the gall-bladder region. His liver was felt about half an inch below the costal margin. At 11 a.m. he passed 190 c.c. of mahogany-coloured urine containing 55 mg. per cent. of oxyhaemoglobin with a pH of 5·3 (electrometric). The deposit revealed brown granular casts and amorphous debris, and there was a considerable amount of albumin. He subsequently passed 210 c.c. of urine at 3 p.m. containing 108 mg. per cent. of oxyhaemoglobin and 855 mg. per cent. of methaemoglobin. At 11 p.m. a further 40 c.c. was passed containing 2·3 mg. per cent. of oxyhaemoglobin and 4·70 mg. per cent. of methaemoglobin. The pH remained at 5·3. His blood pressure was 120/90; erythrocytes 1·8 million per cu. mm., leucocytes 50 000 per cu. mm.

Careful cross-examination both of the patient and his wife excluded any history of malaria, or malaria-like illness or any dosage of prophylactic quinine and slides examined at that time, and repeatedly throughout his illness, revealed no evidence of malaria parasites. In addition, there was no history of previous administration of any of the sulphonamide drugs. His past history had nothing of any significance.

The temperature fluctuated around 101° F., with a pulse rate of 100. The diagnosis of acute intravascular haemolysis associated with the administration of sulphanilamide was made and treatment and investigation instituted on that basis.

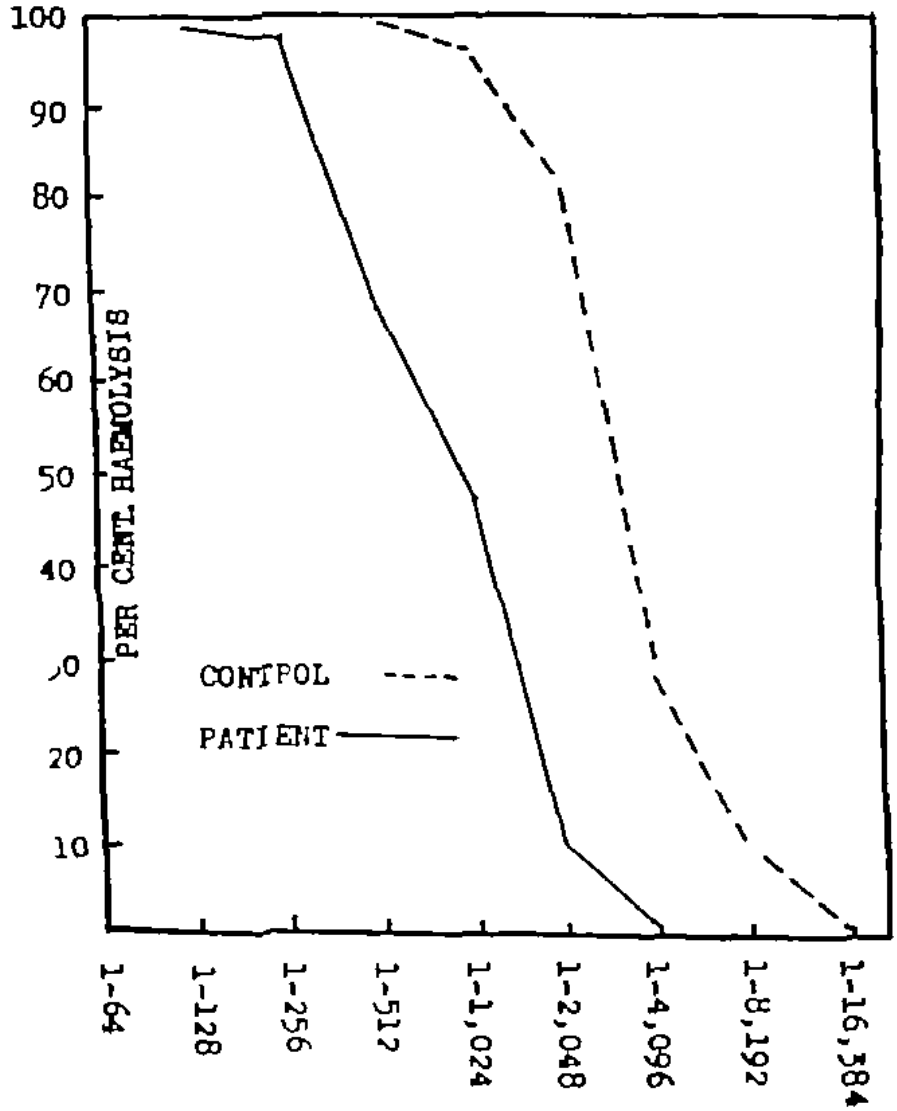
Intravenous glucose saline was commenced, and an hour later 500 c.c. of Group "O" blood were given. The patient's group was "O" and direct compatibility tests were performed before and after transfusion. After 300 c.c. had been administered the patient had a very severe rigor but complained of no pain or sensation in the chest or lumbar region. The temperature rose to 104·4° and the transfusion was stopped. He recovered from this crisis within a few hours.

21st February.—The patient was drowsy; total urinary output for the day was 60 c.c. containing both oxyhaemoglobin and methaemoglobin (see Table I, p. 305). Diathermy was given to both kidneys for 10 minutes with no results. A continuous intravenous glucose saline was running to which had been added 10 grammes of sodium bicarbonate. The effect of this single administration of alkali, as will be seen in the table, was to lift the pH of the urine from 5·0 to 7·8 (electrometric). B.P. was 120/70. A 500 c.c. blood transfusion was given through a Y-tube together with saline with no untoward consequences. Blood urea, 183 mg. per cent. By 4 p.m. B.P. 190/100; temperature 99° to 100° F., pulse racing. At 6 p.m. a further 500 c.c. blood transfusion was started. B.P. 150/70; blood urea, 278 mg. per cent.

Throughout this period he took fluids freely by mouth (Table I) but had waves of nausea and he vomited small quantities of bile stained fluid. Excessive perspiration was a marked feature of his condition. Details of fluid intake and output are shown in Table I

22nd February—After a good night he passed, at 6 a.m. 8 c.c. of much lighter urine containing only traces of oxyhaemoglobin. B.P at 8.30 a.m. 160/65 500 c.c. of blood given and at 11 a.m. he passed 10 c.c. of perfectly clear urine Erythrocytes, 2·09 million per cu. mm. leucocytes 32 000 per cu. mm. and blood urea, 263 mg per cent

GRAPH 1—LYSO-LECITHIN FRAGILITY



The plasma contained 291 mg per cent. of methaemalbumin (623 mμ) and 90 mg per cent. of oxyhaemoglobin (Hartridge reversion spectroscope)

23rd February—Passed 45 c.c. of clear urine was stuporous with bouts of excitement, there was a deterioration in his condition. B.P was 160/55 blood urea 371 mg per cent. A complete blood examination done on this day is given in Table II and for the other days in Table V

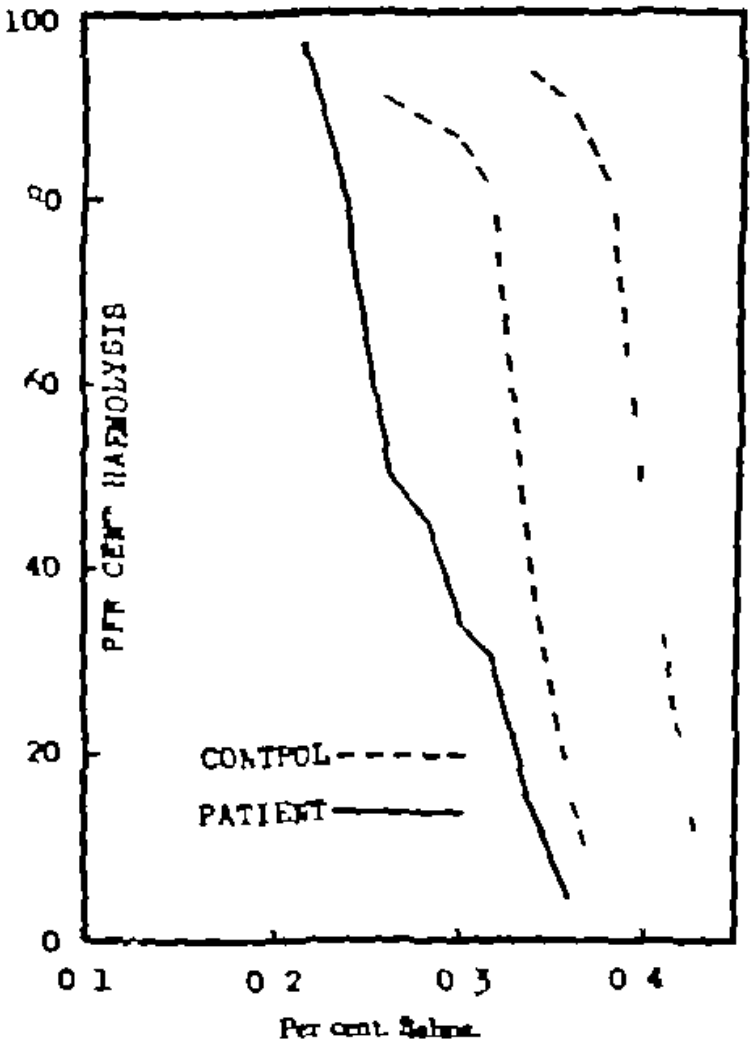
The fragility of the red cells to saline and lyso-lecithin was as indicated in Tables III and IV and Graphs 1 and 2 and Price-Jones curve in Graph 3 The Kahn test and blood culture were both negative

24th February.—Little change: blood urea 358 mg. per cent. B.P. 175/35: erythrocytes, 3·4 million per c.mm. and leucocytes 30,000. Rales were heard at the right base and a small patch of consolidation. Passed 45 c.c. of clear urine.

25th February.—The jaundice was diminished and the mind rational. Blood urea, 486 mg. per cent. Urinary output for the day was 25 c.c.

26th February.—The improvement seemed maintained and he passed a little more urine. Blood urea was 512 mg. per cent. and the B.P. 140/100. Later in the evening, however, the patient gradually collapsed and died.

GRAPH 2.—SALINE FRAGILITY



POSTMORTEM REPORT

Autopsy was performed 5 hours after death, permission having been granted for the thorax and abdomen only.

Thorax.—There was no fluid in either pleura. Both lungs showed subpleural petechiae and the base of the right lung was oedematous. The heart and pericardium appeared normal.

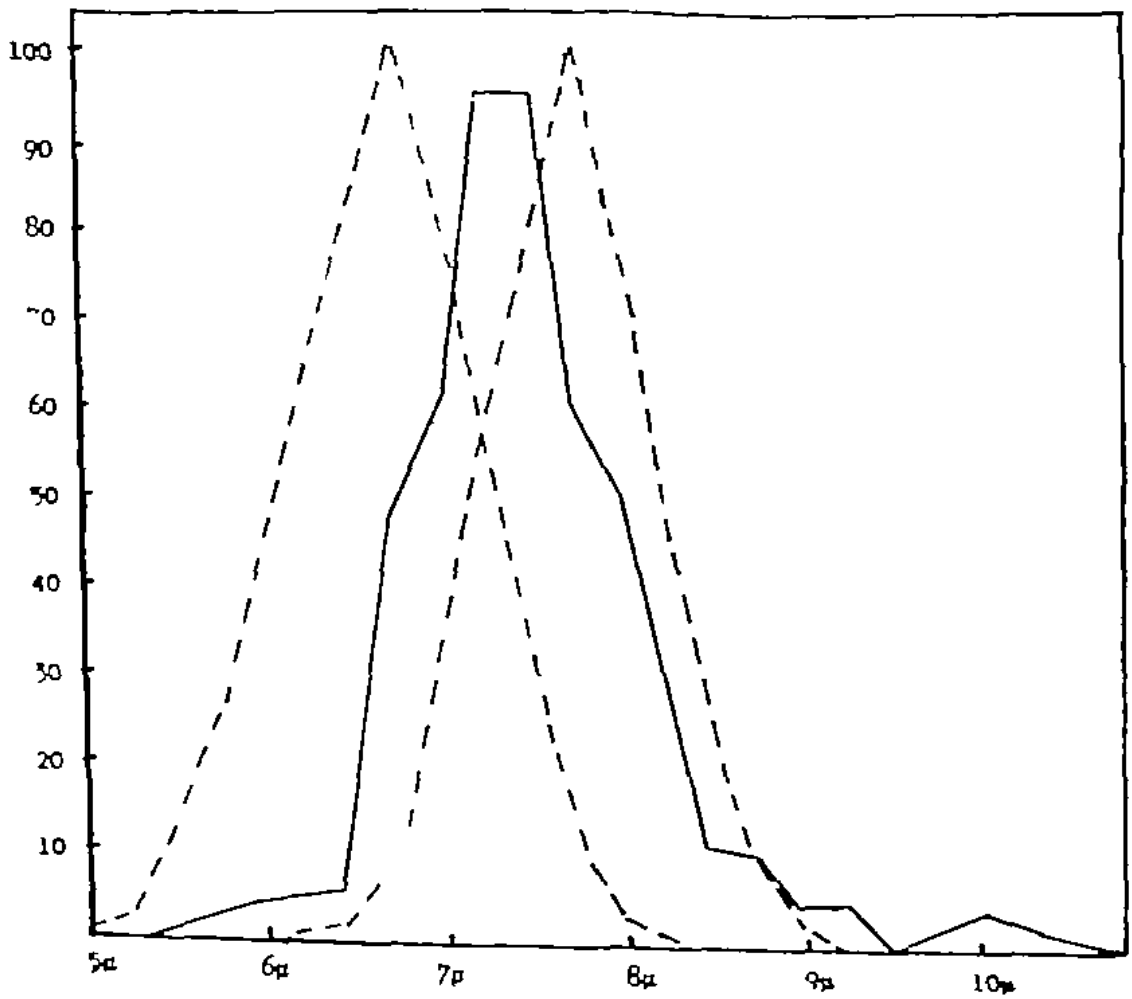
Abdomen.—Liver was enlarged and hard. The gall-bladder wall was

oedematous and fully half an inch in thickness The bladder was full of cheesy black bile but there was no obstruction in any part of the duct system.

The pancreas was hard and the consistency was woody

The kidneys did not appear grossly enlarged and the capsule stripped easily On section they were a deep purple in colour extremely congested and oedematous, and it was barely possible to distinguish cortex from medulla. The renal pelvis ureters and bladder were all empty, patent and of normal appearance.

GRAPH 3 — PRICE JONES CURVES



The suprarenal glands were small and atrophic. The spleen was slightly enlarged congested, hard and of a deep purple colour Except for a small encapsulated abscess in the left tonsil all else was normal. Tissue was removed from all organs for histological examination

Detailed histological study of this case will form the subject of a separate report elsewhere but a brief description of kidney liver and gall bladder is of interest.

In the kidney the outstanding feature was the wide separation of the tubules by intensely oedematous tissue, in which the reticular fibres were unusually obvious. Lying in the oedematous mass were pools of coagulated lymph and focal aggregation of plasma cells, especially marked in the region of the large calyces. The oedema nowhere tended to compress the tubule. In the proximal convoluted tubules the epithelium was degenerated and the nuclei irregular and of bizarre shapes. In many areas desquamated cells from the convoluted tubules were seen to be lying free in dilated tubules surrounded by eosinophilic debris in such tubules the basement membrane was thick and opaque.

The majority of the glomerular tufts with their epithelium, and capsular spaces, appeared normal.

There was a great difference in the appearance of the kidney in the paraffin and frozen material. In the former as stated above, the tufts and capsular spaces appeared to be normal. In the frozen material, on the other hand, where the distortion due to dehydration is absent the glomerular tufts almost completely filled the capsule, and the spaces were consequently very much reduced in size The tubular epithelium in the frozen sections showed much less separation from their basement membranes and the granular debris almost filled the lumen with loose masses which by no means blocked the tubules. It seems to us that in investigating the histological changes that take place in these anuric conditions the frozen material is a better guide to what is taking place than are paraffin sections.

The distortion due to dehydration, as will be seen from Plate Figs. 1 and 2, produces a very misleading picture of the changes going on in the various kidney elements.

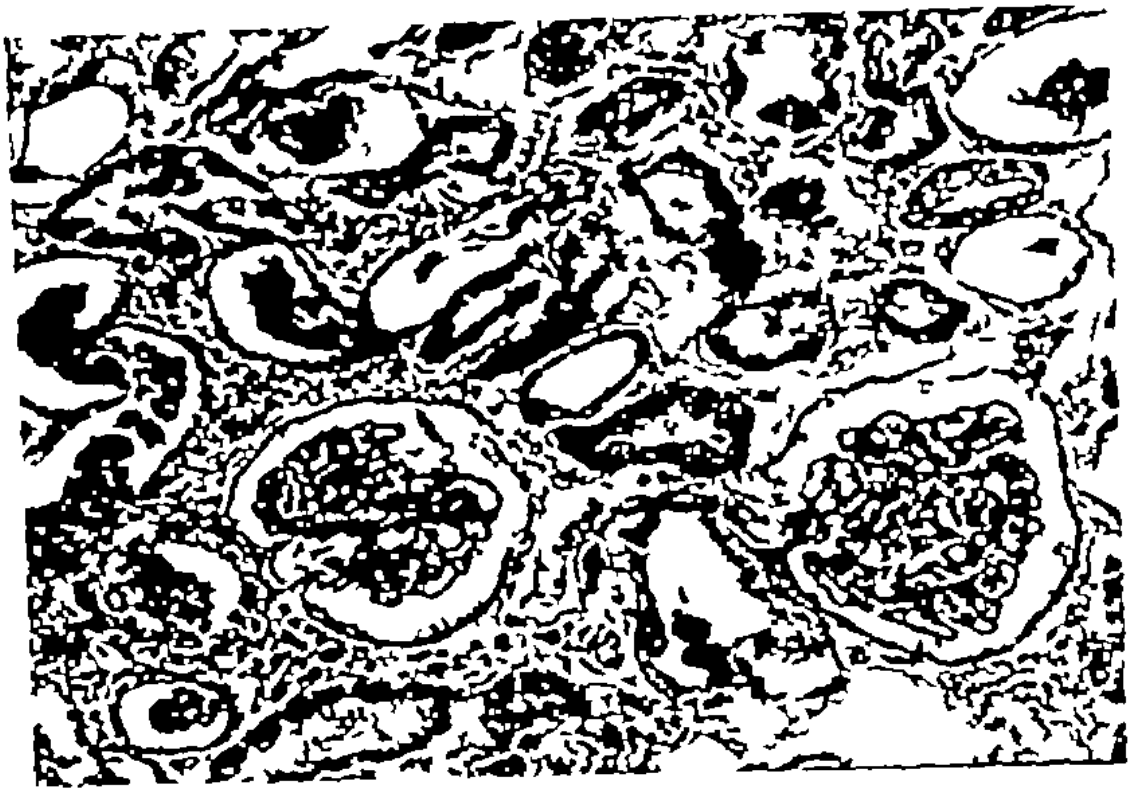
The dominant feature about the liver was the total absence of pigment from the Kupffer cells, and it is difficult to conceive that this could be due to the rapid formation of bilirubin. Some failure of the reticulo-endothelial system may have been responsible.

In addition the central vein was distended, and the hepatic cells in the related trabeculae were atrophic the reticulum was pronounced and appeared to be separated from the liver cells. The gall-bladder showed no catarrhal changes or desquamation of the epithelium. Goblet cells were seen in great profusion. Oedema of all layers was intense and there were many histiocytes loaded with pigment.

Discussion

In deciding whether a case is haematuria or haemoglobinuria, spectroscopic examination of the plasma and urine for the detection of haemoglobin or its derivatives is essential. The existence of red blood cells in the urine will at once cast doubt on a diagnosis of haemoglobinuria. In examining urine for haemoglobin the fluid should be freshly passed so as to reduce the chances

FIG 1



Kidney Section × 200 (Paraffin material)

FIG 2

Kidney Section × 200 (Frozen material)

To face page 310]

of destruction of any red cells and thus give rise to a false diagnosis of haemoglobinuria. The presence of methaemoglobin in the urine should immediately lead to the suspicion of true haemoglobinuria A haemolysis that is sufficient to produce a haemoglobinuria will show a haemoglobinaemia if the blood is taken during or immediately before the access of haemoglobinuria. The presence of a haemoglobinaemia is the final court of appeal in deciding whether we are dealing with haemoglobinuria or haematuria. In addition to the presence of oxyhaemoglobin in the plasma other pigments indicative of an intravascular haemolysis will generally be found, such as haemobilirubin and methaemalbumin. In addition, Schumm's test will be positive, and this is regarded (FAIRLEY 1941) as indicative of amounts of methaemalbumin which are too small to be detectable by spectroscopic examination, even in great stratum thicknesses All these haemoglobin derivatives have been found in conditions where intravascular haemolysis has occurred, such as blackwater fever haemolytic jaundice, incompatible transfusions, and poisoning by various drugs

In the case reported here all three pigments were present, as well as intracorpuscular methaemoglobin thus establishing that the haemoglobinuria was due to a pre-existing intravascular haemolysis. The pigment estimations were carried out by means of a Hartridge reversion spectroscope.

There is a certain amount of confusion concerning the types of pigments present in the haemolyses that sometimes accompany the administration of sulphonamides Some authors have stated that they find neither methaemoglobin nor sulphaemoglobin even though large amounts of sulphonamides have been given (CARNAVA, 1940) MARSHALL and WALZL (1937) pointed out that since the oxygen carrying capacity of the blood in such drug toxicities is low when compared with its iron content, there must be some non functional iron containing pigment present in the blood and they suggested methaemoglobinaemia, and later identified this pigment but did not rule out the possibility of sulphaemoglobin also being present.

The recent spectrophotometric, and spectrographic work of HARRIS and MICHEL (1939) and FOX and OTTENBERG (1941) and FOX and CLINE (1940) has settled the question of pigment metabolism in these sulphonamide toxicities. The findings of these workers has established that intracorpuscular methaemoglobin plasma methaemalbumin, oxyhaemoglobin, and haemobilirubin are all present, and that the urine may contain either or both oxyhaemoglobin and methaemoglobin. A much rarer pigment is sulphaemoglobin No sulphaemoglobin was found in the present case.

It is recognized that a greater or lesser degree of methaemoglobinaemia is consequent upon sulphonamide administration. There appears to be no relation however between the occurrence of methaemoglobinaemia and sulphaemoglobinaemia. The latter is not positively correlated with blood sulphonamide levels but is dependent on a third factor, viz sulphides hence desirability of restricting sulphur-containing foods during sulphonamide therapy NIBLOCK

(1941) has, however pointed out that diets containing sulphur have probably no relation to the development of sulphaemoglobinaemia. Methaemalbuminaemia is dependent upon the extent and duration of the haemolytic process, and if this is small and of short duration the haemoglobin liberated will be dealt with by the intracorpuscular disposal mechanism, and haemobilirubin will increase. If on the other hand, the haemolysis has been large and acute, or long continued then the extracorpuscular disposal mechanism will come into play and the free haemoglobin in the plasma will be broken down to haematin and will then combine with plasma cystalbumin to form methaemalbumin. (FAIRLEY 1941)

A point of considerable interest is the presence of intracorpuscular methaemoglobin in the sulphonamide haemolyses and its absence so far as is known in blackwater fever in the other intravascular haemolyses nothing is known concerning its presence or absence.

Methaemoglobin is an oxidation product of haemoglobin, the iron moiety being converted from the divalent to the trivalent state. Such conversions can be accomplished by means of a number of oxidising agents, such as potassium perchlorate which will perform this oxidation both *in vivo* and *in vitro*

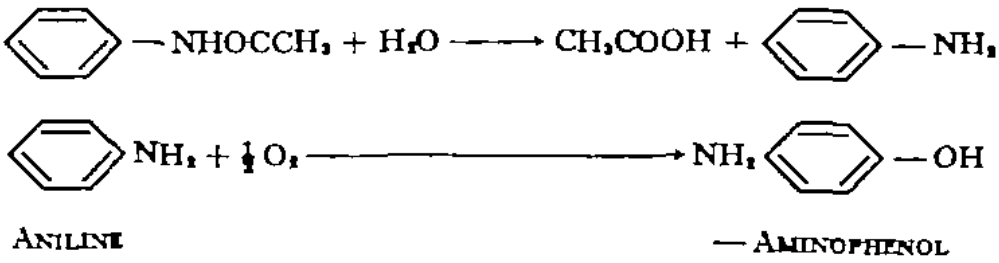
There are, however a number of substances such as aniline, acetanilide, plasmoquine, nitrobenzene, as well as sulphonamides that are not oxidising agents *per se* but which do produce methaemoglobinaemia (HEUBNER 1913 HEUBNER *et al.*, 1923 FOY and KONDI 1938). In the case of aniline and acetanilide the production of *p*-aminophenol and its derivatives, such as quinoneimine, have been shown to be responsible for methaemoglobin production (HEUBNER & SCHWIDTER, 1936 BERNHEIM, 1942)

Whether the production of *p*-aminophenol is responsible for the methaemoglobinaemia in the case of sulphonamides is uncertain RHAMNGTON (1939) has suggested that it may be and that semiquinones may play a part in the oxidation of haemoglobin to methaemoglobin. JAMES (1940) states that *p*-aminophenol occurs in the urine of animals given sulphonamides. It has, however been pointed out by THORPE and his co-workers (1941) that the tests used for the identification of *p*-aminophenol were not specific, and on theoretical grounds it seems unlikely that the NH_2SO_2 group could be removed from the sulphanilamide ring *in vivo* and allow the formation of the end products that are reputed to be responsible for the production of methaemoglobin.

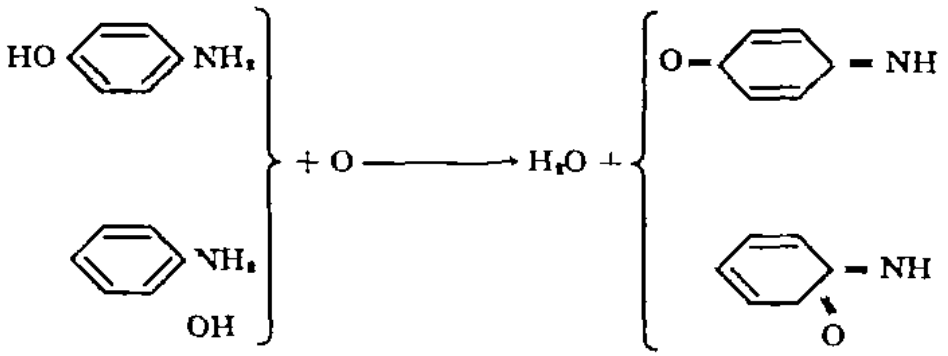
Methaemoglobincythaemia is of less serious consequence than sulphaemoglobincythaemia since the former reverts to oxyhaemoglobin in a few days and its disposal can be hastened by means of methylene blue administration. It is not known whether the acceleration of methaemoglobin disappearance by means of methylene blue is due to direct reduction of the methaemoglobin by methylene blue, or to the fact that the substance responsible for the oxidation of haemoglobin to methaemoglobin reacts with methylene blue instead of with haemoglobin. Irrespective of what mechanism is involved, it should be possible,

theoretically, for any substance capable of facile reversible oxidation and reduction to bring about the same result as does methylene blue. A very suitable substance from this point of view would be ascorbic acid on account of its high reactivity and non toxicity In this connection it should be mentioned that glutathione which is present in high concentration in red blood cells (MORRISON and WILLIAMS, 1938) may be one of the mechanisms that is responsible for preventing the accumulation of methaemoglobin *in vivo* the known ability with which certain of the sulphonamides penetrate the red cells may upset the normal glutathione-methaemoglobin preventing mechanism, and permit the appearance of intracorpuscular methaemoglobin. In a future paper we are dealing with the question of methaemoglobin formation in certain of the intravascular haemolyses and further discussion of this will be left until then

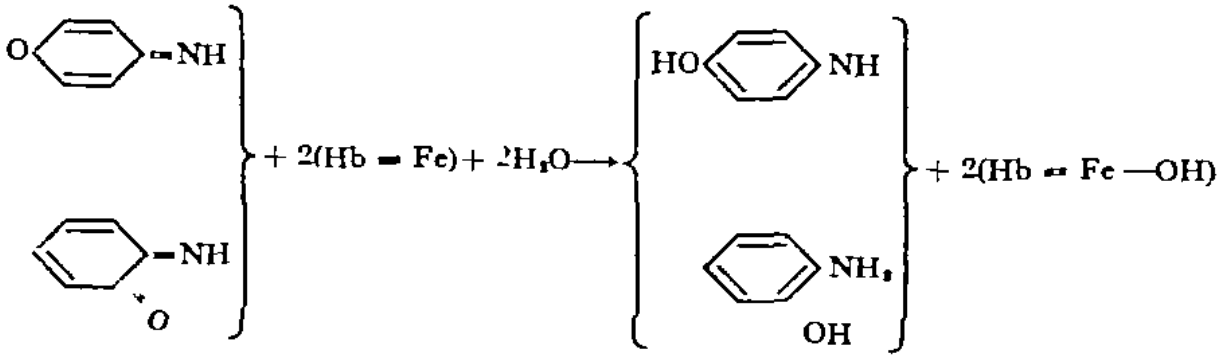
The reaction can be represented by the following scheme —



ANILINE — —AMINOPHENOL



—AMINOPHENOL + OXYGEN ⟶ WATER + QUINONEIMINE



QUINONEIMINE + HAEMOGLOBIN + WATER ⟶ —AMINOPHENOL + METHAEMOGLOBIN

TABLE
BLOOD

Date 1943 Feb	R.B.C. Millions per c.mm.	Hb. % Sahli	W.B.C.	Reticulocytes %	Haematocrit %	M.C.V μ^3
20	1·8 (12 m.)	42	49,000	—	20	111
1	2·3 (11 m.)	60	80,000	—	—	—
22	2·08 (8.30 a.m.)	75	24,000	—	23	100
23	2·0 (10.20 a.m.)	55 7·5 gm. %	23,000	1 10	— 22	110
24	3·4 (12 midd.)	—	30,000	—	—	—
25	3 (11 m.)	49	23,000	—	—	—
26	2·2 (12 midd.)	63	22,000	10	—	—

Very little is known concerning the means by which methaemoglobin makes its appearance in the urine that it is not related to plasma methaemalbumin, or intracorpuscular methaemoglobin seems fairly clear or that pH changes and ionic concentration of the urine are not the only or most important factors at work.* In crush injuries myohaemoglobin has been reported in the urine In addition to the haemolysis in these sulphonamide toxicities there occurs in some cases a great reduction in the output of urine, similar to that which is often present in blackwater fever and the other intravascular haemolyses, and which may pass into complete anuria. The majority of such cases of anuria that occur in the sulphonamide toxicities have been shown to be due to mechanical blockage of the upper parts of the urinary tract with crystalline derivatives of the drug, which may lead to traumatic haematuria and anuria. There are, however on record a number of cases where such mechanical blockage and injury can be ruled out, and in which the explanation of the anuria must be sought elsewhere

We have dealt in an earlier paper (FOY ALTAMAN BARNES and KONDI 1943) with the renal failure that occurs in such haemolytic conditions as blackwater fever incompatible transfusions and sulphonamide toxicity and with that which occurs in crush injuries. Similar renal findings have recently been

* RUSSELL (1938 and 1939) has shown that urochrome and certain other urinary pigments will convert haemoglobin into methaemoglobin *in vitro* in the absence of oxygen

INDINGS.

Sedimentation 1 hour	Blood Urea Mg %	Plasma or Serum Pigments			Fragility
		OxyHb.	MetHb.	MetAlb	
74 mm.	—	+++	Nil	+	0 34–0·22
—	193 (11 a.m.) 278 (5 p.m.)	+++	Nil	+	—
68 mm.	263	90 mg %	Intra-corpuscular	29 1 mg %	0 28–0 28 Incomplete
—	371	Nil	Nil	97 5 mg %	—
—	358	Nil	Nil	Nil	0 36–0·22
—	468 (11 a.m.) 494 (8 p.m.)	Nil	Nil	Nil	—
—	51*	Nil	Nil	Nil	0·34–0·28 Incomplete

described by YOUNG (1942) in utero-placental damage and by MCLETCHIE (1943) in severe vomiting

In the case reported above there were changes in both the tubules and the glomeruli, although abnormality of the latter was only visible in the frozen sections a point worth further investigation since most authors have described no glomerular changes in the material dehydrated by fixatives.

The fluid intake and urinary output in the present case is shown in Table I together with data regarding the blood transfusions and urine analyses. As will be seen, there was a steadily diminishing flow of urine, in spite of an adequate fluid intake. There appeared to be no relation between the urinary flow and variations in systemic blood pressure as will be seen from Table VI

TABLE VI.

BLOOD PRESSURES.

Date	S/D	Time.	Date.	S/D	Time.
20	1*0/70	—	2*	160/65	—
1	1*0/70	10 a.m.	23	160/55	8 30 a.m.
21	190/100	3 p.m	24	190/85	6.30 a.m.
*1	150/70	5 p.m.	24	175/55	2 p.m.
*1	140/70	8 p.m.	2.	175/80	8.30 a.m
22	160/65	8.30 a.m.	26	140/100	8 30 a.m
22	160/85	—			

It appears that the renal failure that occurs in all these conditions has a similar basis, and cannot be explained as a result of the operation of any single factor such as blockage of the lumina of the renal tubules with products of haemoglobin precipitated from an acid urine (Baker and Dodds, 1925). Recent work seems to indicate that a great many factors may be involved in the renal failure in these conditions among which may be mentioned diminished glomerular infiltration due to a variety of causes, such as dehydration, actual or physiological, disturbances in acid-base-electrolyte-water balance and upsets in the permeability of the glomerular membrane, etc.

Reduction in blood flow might especially affect the tubules on account of their high oxygen requirements and lead to degenerative changes followed by upsets in tubular reabsorption and concentration. These changes in glomerular filtration and tubular reabsorption and their concomitant sequelae would lead to piling up of necrosed matter and haemoglobiniferous material in the tubules, and thus any blockage would be the result of antecedent factors, and not itself the cause of the anuria or azotemia (Foy *et al.* 1943).

Bradford and Shaffer (1942) and Gross, Cooper and Morningstar (1942) have described the appearance of the kidneys in cases of death from sulphonamide haemolysis and anuria and have noted cloudy swellings, and degenerative changes in the tubular cells, as well as glomerular changes which they consider are the cause of the anuria.

We have no explanation for the severe reaction that occurred during the first transfusion. Since it occurred after only 300 c.c. had been given it might point to low titre Landsteiner group incompatibility. The large number of successful transfusions that have been given by this unit would seem to rule out pyrogens or insufficiently cleaned apparatus. Rothstein and Cohn have stated that iso- and pan-agglutination occurs in some cases after sulphonamides, but neither in this nor in his cases can the factors mentioned above be ruled out.

It should be borne in mind that such auto- and pan-agglutination is common in many severe anaemias as well as in liver diseases (Wiener, 1939) and it is not necessary to incriminate sulphonamides to account for these phenomena, in either this or Rothstein's case. Agglutination and spherocytosis are generally regarded as precursors of haemolysis, and according to Hall and Castle (1940) are associated with changes in the osmotic fragility of the red cells to saline. As has been pointed out elsewhere (Foy and Kondi, 1943) it is not always possible to associate changes in osmotic fragility with either in vivo haemolysis or spherocytosis so far as blackwater fever is concerned. That in some conditions changes in the diameter thickness ratio may be linked with variations in osmotic fragility is probably true, but it cannot be regarded as an invariable linkage. Hall and Castle consider that in the haemolyses that occur in icterus gravis neonatorum, haemolytic jaundice, and after some drugs, circulating haemolysins are not the cause of the red cell destruction, but that there is some defect in the red cell itself that renders it more liable to haemolysis,

following stasis, agglutination and spherocytosis That the changes considered by these workers are secondary to more fundamental ones occurring in the cells environment is shown by the fact that removal of the spleen in haemolytic jaundice stops the periodic haemolyses but leaves the fragility of the red cells unchanged. In blackwater fever normal red cells transfused into a haemolysing case are broken up just as are the patients own cells (FOY and KONDI 1941) and in icterus gravis neonatorum Rh factors are probably behind the haemolysis That the situation is however by no means a simple one is brought out by the recent work of CRUZ and his colleagues (1941) who have shown that red cells labelled with radio-active isotopes of iron are more likely to be destroyed if young than if they are more mature.

ANTOPOL *et al* (1941) state that in rats given sulphonamides there is an increase in the resistance of the red cells to saline whether the increase seen in our case is due to the same cause is impossible to say in COOLEY'S anaemia the same phenomenon is present (WINTROBE, 1942)

The greatly increased resistance to both saline and lyso-lecithin noted in the present case was not associated with any abnormality in the Price-Jones curves, and the mean cell diameters, volumes thicknesses and ratios were all within normal range, as will be seen from the charts.

The volume thickness index and diameter thickness ratio appear to be intermediate between normal and blackwater fever if HADEN'S figures for normal values are taken As, however HADEN gives only absolute values, and not normal ranges comparisons are not of much value. The figures in the present case are very different from those obtained in haemolytic jaundice (FOY and KONDI 1943)

The surface areas calculated from Knoll's formula ($0{\cdot}64 \times \pi D^2$) are normal

SUMMARY

1 Attention is directed to the resemblances and differences in blood pigment metabolism in such conditions as blackwater fever haemolytic jaundice, and the intravascular haemolysis that sometimes occurs after sulphonamides It is noted that intracorpuscular methaemoglobin occurs after sulphonamides plasmoquine and acetanilide but does not occur in blackwater fever so far as is known. Oxyhaemoglobin methaemalbumin and haemobilirubin are common to all of the intravascular haemolyses

It appears that *p*-aminophenol or a derivative thereof is responsible for the methaemoglobinaemia that occurs after aniline and acetanilide, whether or not similar metabolites are responsible in the case of sulphonamides and plasmoquine seems uncertain

2. In the present case there was an acute massive intravascular haemolysis accompanied by the presence of plasma oxyhaemoglobin methaemalbumin, and haemobilirubin as well as intracorpuscular methaemoglobin and a profound fall in the red cell count.

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TECHNIQUE AND INTERPRETATION OF THE WEIL-FELIX TEST IN TYPHUS FEVER*

BY

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From the Emergency Public Health Laboratory Service

The following notes have been prepared in response to requests for a brief account of the technique and interpretation of the Weil-Felix reaction Much of the recent work on the typhus group of fevers has been published in English but the extensive earlier work on the Weil-Felix reaction in classical louse borne typhus appeared in foreign literature and is known to the younger generation of clinicians and pathologists in this country merely from the scanty references given in the textbooks Even the article on typhus fever in *A System of Bacteriology* (FELIX 1930) does not contain adequate information on the clinical and epidemiological aspects of the test.

The three serological varieties of *Proteus* X known as OX19 OX2 and OXK are no longer the only reagents by means of which the serological diagnosis of the different varieties of typhus can be made. Suspensions of rickettsiae can now be obtained in relatively large quantities by growing these organisms in the yolk sac of the developing chick (COX, 1938) or in the lungs of infected rats and mice (CASTANEDA, 1939) Purified rickettsial suspensions are now being tried in agglutination and complement fixation tests with typhus sera in various parts of the world and there can be little doubt that this work will lead to important advances in the serology of the typhus group

Rickettsiae possess heat labile and heat-stable antigens (CASTANEDA and ZIA, 1933) and sera from typhus patients contain, or may contain the corresponding two kinds of antibody In the future an improved method of serum

* A report to the Medical Research Council

diagnosis of the typhus fevers is, therefore likely to be based on the separate estimation of the two different rickettsial antibodies, much in the same way as the enteric fevers are now diagnosed by the demonstration of H and O agglutinins for each of the members of the typhoid paratyphoid group Even a third type of reagent is required in the so-called Vi agglutination test for the detection of chronic typhoid and paratyphoid carriers So far three specific O antigens of typhus rickettsiae have been identified which these organisms share with the three serological varieties of *Proteus* X. The three O antigens are available in the most convenient form in suspensions of *Proteus* OX19 OX2 and OXK. What is needed are suitably prepared reagents for the estimation of the antibodies to the heat labile rickettsial antigens. It was mentioned in a previous paper (FELIX 1942) that the heat-labile and heat-stable antigens of *Rickettsia prowazeki* behave similarly to the Vi and O antigens of *Bact typhosum* The heat labile antigen of rickettsiae inhibits the interaction between the heat-stable antigen and its corresponding antibody in the same manner as the Vi antigen does in the case of the O antigen of the typhoid bacillus. The results so far obtained with rickettsial agglutination tests are rather confusing Some workers have reported almost complete parallelism between agglutination of *R prowazeki* and *Proteus* OX19 whereas others obtained quite different results. This seems to indicate that some of the rickettsial suspensions, as at present prepared, are not entirely insensitive to the O antibody and do not therefore, serve as pure reagents for the antibody to the heat-labile rickettsial antigen. Nevertheless, it has already become possible by means of complement fixation and agglutination tests with rickettsial suspensions to distinguish between some of the varieties of the disease which give overlapping reactions to the *Proteus* OX antigens (BENGTSON and TOPPING, 1942 PLOTZ, 1943 VAN ROOYEN and BEARCROFT 1943 STUART HARRIS REITTIE and OLIVER, 1943) The relative usefulness of diagnostic tests with suspensions of rickettsiae and *Proteus* OX strains in the early diagnosis of cases and in the retrospective diagnosis of missed ambulatory patients is a problem which remains to be investigated.

For the present, however most pathologists must continue to rely on the agglutination test with *Proteus* OX antigens as the sole test available for the routine diagnosis of cases of typhus fever and for carrying out epidemiological surveys in localities where the disease is prevalent. The technique and interpretation of the test and its application by the clinician and epidemiologist are discussed in this paper mainly in relation to the louse borne typhus of type OX19 the variety of the disease that is most dreaded. Louse borne typhus is usually referred to as epidemic typhus but it should be borne in mind that the disease is endemic in many parts of the world and gives rise to widespread epidemics only under conditions that favour louse infestation. The term louse-borne typhus, used throughout this paper applies to both the epidemic and the endemic form of the disease. The other typhus like fevers are dealt

with in less detail and only those varieties are discussed here which occur in the countries that are at present or soon may become a theatre of operations. Table I shows the fevers of the typhus group subdivided into three serological sub-groups according to the agglutination reactions obtained with the three different *Proteus* OX antigens

TABLE I

PROVISIONAL CLASSIFICATION OF THE TYPHUS GROUP OF FEVERS.

	Immunological Sub-group		
	Type OX19	Type OXK	Type Undetermined
Name of disease	Classical epidemic typhus Tabardillo (Mexico) Brill's disease (U.S.A.) Endemic typhus of U.S.A. and Australia, Greece Syria Manchuria Malaya (shop typhus) India Burma, Philippines, Hawaii Toulon (fièvre nautique) etc.	Tsutsugamushi fever of Japan, Formosa, Malaya, and Dutch East Indies Scrub typhus of Malaya, Dutch East Indies India French Indo China Australia	Spotted fever of Rocky Mountains Spotted fever of eastern U.S.A. São Paulo typhus Fièvre boutonneuse (Mediterranean) Fièvre exanthématique of Marseilles Febbre erruttiva (Italy) Tick bite fever of South Africa Epidemic and endemic typhus of South Africa Tick borne typhus of India, Kenya, etc.
Vector	Lice and rat fleas	Mites	Ticks lice, and rat fleas
Reservoir of virus	Rats Man	Field mice and rats	Rodents. Dogs ? Ticks Man
Agglutination	OX19 +++ OX2 + OXK —	OX19 — OX2 — OXK +++	OX19 + OX2 + OXK +

LOUSE BORNE TYPHUS TYPE OX19

TWO DIFFERENT FORMS OF THE CURVE OF AGGLUTININ PRODUCTION

Soon after the introduction of the Weil Felix test in routine diagnosis it was observed that cases of louse borne typhus show two different types of the curve of agglutinin formation One type is characterized by the early appearance of agglutinins, high maximum titres and the persistence of a raised titre

for a long time after recovery. In the second type the agglutinins appear comparatively late in the disease, reach only low titres and disappear early during convalescence. A number of reaction curves are reproduced here from earlier papers (Felix, 1-19, 1917), since the figures demonstrate better than words how great is the difference between the two types of antibody response.

The cases listed in Table II came from an outbreak in a labour camp which was under careful medical supervision and some of the patients had been admitted to hospital as contacts even before the onset of symptoms (e.g. case No. 12). Accurate case histories were therefore available and fairly complete curves of the development of N/10 agglutinins were obtained. The cases recorded in Table III belonged to a series of 310 typhoid cases that had been encountered in Constantinople in 1916-17. The following conclusions were drawn from these observations:

(1) The majority of cases of house-borne typhoid, approximately 75 per cent. of cases, show a significant N/10 reaction on or before the 4th or 5th day of illness, and the maximum titre reached shortly before or after defervescence are very high, usually over 1 : 2000.

(2) The remaining 25 per cent. of cases show a positive reaction about the 6th or 7th day; in exceptional cases later still, and the maximum titre reached are very low (usually below 1 : 500).

(3) The type of the curve of agglutinin formation is related to the clinical course of the disease. There is no hard and fast rule but the relationship may be expressed in the simplest way as follows:

(a) The cases of moderate severity generally respond with high titres.

(b) The most severe cases, including the cases that succumb to uncomplicated typhoid infection, have very low titres.

(c) The milder cases, including the abortive cases and "suppressed" infections, may have either very low or very high titres.

Other workers who had a considerable experience of typhoid during the war of 1914-18 put the cases between cases giving a high titre and those giving a low-titre reaction approximately in the order of 2 : 1 (Zlocisti, 1917; Ott, 1918; Wolff, 1922).

It is of course not possible to draw a clear-cut line of demarcation between the two groups of agglutinin response. Nature does not draw the sharp distinctions that are so desirable for our purposes, and thus border-line cases occur which have an intermediate type of curve. It is, however, clear from the four examples given in Tables II and III that the difference between the maximum titres attained in the two groups is so great that it is unreasonable even to prepare a graph using the same scale for the two types of reaction curve. It is futile to attempt to construct a curve of "average titres" compiled from observations on a large number of cases belonging to the two groups. Such attempts have been made recently in this country and abroad, but they are bound to obscure rather than elucidate the true picture of the rise and fall

TABLE II

SHOWING AGGLUTININ CURVES IN CASES OF LOUSE BORNE TYPHUS OBSERVED IN POLAND DURING 1916
(Abstracted from paper by A. FELIX, 1916 *Wien. klin. Wschr.*, 29 873)

Case No.	Clinical Data.	Serum Examined	Agglutination with		Positive X19 Reaction first observed on
			Proteus X19	*Proteus* X2	
1	Onset April 28 Rash appeared May 1 Temperature normal „ 11	May 1 „ 3 „ 6 „ 9 „ 12 „ 19 „ 27 June 6	500++ 2,000++ 10,000++ 50 000++ 20 000++ 5 000++ 5,000++ 1 000++	25− 25− 25++ 50+ 25++ 25− 25− 25−	4th day of illness (1st day of rash)
2	Onset April 28 Rash appeared May 1 Temperature normal „ 6 (Abortive case)	May 1 „ 3 „ 6 „ 12 „ 19 „ 27 June 6	2,000+ 5,000++ 7 500+ 2,000+++ 2,000+ 1 000++ 500++	50+ 50+++ 50+++ 25+++ 25++ 25− 25−	4th day of illness (1st day of rash)
4	Onset May 2 Rash appeared „ 6 Temperature normal „ 15	May 4 „ 5 „ 7 „ 9 „ 12 „ 19 „ 27 June 6	50++ 50+++ 500++ 5 000+ 10 000++ 20 000++ 2,000+++ 1 000++	25− 25− 25− 50++ 50+ 50+ 25− 25−	3rd day of illness (Two days before rash)
10	Onset May 28 Rash appeared „ 30 Temperature normal June 13	May 30 „ 31 June 2 „ 6 „ 10	25+++ 50++ 200++ 1 000+++ 5 000+	25− 25− 25− 50++ 100+	3rd day of illness (1st day of rash)
12	Onset June 1 Rash appeared „ 4 Temperature normal „ 11	May 31 June 4 „ 5 „ 8 „ 10	25− 50+++± 500++ 7 500++ 2,000+++±	25− 25− 25− 50++ 100+	4th day of illness (1st day of rash)
14	Onset May 10 Rash appeared „ 14 Temperature normal „ 23	May 11 „ 14 „ 15 „ 16 „ 18 „ 22 „ 27 June 6	25− 25− 25++ 50++ 100++ 200++ 100+++ 50++	25− 25− 25++ 25++ 25+++± 50+ 50++ 25+	6th day of illness (2nd day of rash)
15	Onset May 16 Rash appeared „ 20 Died „ 25	May 19 „ 20 „ 22 „ 23 „ 26	25− 25− 25+++ 50+++ 500+++	25− 25− 25++ 25++ 50++	7th day of illness (3rd day of rash)

TABLE III

SHOWING AGGLUTININ CURVES IN CASES OF LOUSE-BORNE TYPHUS OBSERVED IN TURKEY DURING THE WINTER 1916–17

(Abstracted from paper by A. FELIX, 1917 *Z. ImmunForsch.*, 26 602)

Case No.	Clinical Course	Day of Illness	Titre of Agglutination with *Proteus X19*	Titre of Agglutination with *Proteus X2*	X19 Agglutinin Curve
698	Moderately severe	6	200	0	High-titre curve
		7	1,000	50	
		10	2,000	100	
		12	2,000	100	
		17	2,000	50	
655	Moderately severe	5	500	50	High-titre curve
		7	4,000	80	
		10	10,000	50	
		15	5,000	80	
		19	2,000	50	
		26	2,000	25	
699	Moderately severe	4	200	0	High-titre curve
		6	800	50	
		8	1,000	100	
		11	10,000	200	
		16	5,000	200	
628	Moderately severe	1	0	0	High-titre curve
		2	50	0	
		4	200	50	
		10	10,000	500	
		14	10,000	800	
		21	10,000	800	
611	Moderately severe	5	200	0	High-titre curve
		14	4,000	50	
		22	2,000	50	
		36	1,000	50	
		43	1,000	0	
470	Very severe	11	25	0	Low-titre curve
		13	100	0	
		21	50	0	
		30	5	0	
		39	0	0	
662	Very severe	7	25	0	Low-titre curve
		12	100	50	
		18	100	50	
		24	50	0	
		44	30	0	
541	Very mild	7	25	25	Low-titre curve
		15	50	50	
		21	25	25	
		30	25	25	
578	Very mild	6	50	0	Low-titre curve
		9	50	0	
		19	100	0	
		29	100	0	
		33	50	0	

Titre 0 indicates a negative result in dilution 1 : 25.

of the agglutinin titre in both groups In order to derive full advantage from the use of the diagnostic test it is clearly essential to pay due attention to the distinctive features of the two types of reaction curve.

NORMAL OX19 AGGLUTININS AND RESIDUAL AGGLUTININS DUE TO A PREVIOUS TYPHUS INFECTION

The sera of normal persons contain low titre agglutinins for the *Proteus* X strains even in natives of countries which for generations have been free from typhus. These normal agglutinins are of the O type, as are also those for typhoid and paratyphoid bacilli. The incidence and titres of normal agglutinins for OX19 and OX2 are lower than those for the enteric group of organisms In a series of 1837 control sera from normal persons and patients suffering from various febrile diseases, 7 per cent. agglutinated the strain X19 in a dilution 1 25 and 1 2 per cent. in a dilution 1 50 (see WEIL, 1920) These results were obtained during 1916–18 using live suspensions of the H + O variant of the strain X19 and the fractional titres should, therefore, be multiplied by 2 in order to indicate the figures for the O variant which is now in general use When an O variant is used the degree of O agglutination seen at the 24 hour reading is, as a rule, twice that for the corresponding H + O variant. Most workers fix the limit for normal agglutination with OX19 at 1 100 others prefer to put it at 1 200

In countries with endemic typhus where there is the possibility of persistence in the serum of residual agglutinins due to a previous infection, absolute diagnostic significance cannot be claimed for titres even considerably higher The length of time during which a relatively high OX19 titre persists after the attack depends on the height of the maximum titre that had been attained during the disease. It has been stated in the previous section that the majority of cases of louse borne typhus develop what has been called the high titre curve of agglutinins. In these cases a retrospective diagnosis can usually be made from the agglutination test during 3 or 4 months following the attack of typhus and in some cases even after a much longer interval. On the other hand, those patients whose serum exhibits a low titre curve of agglutinins during the disease may show a negative result in the OX19 test almost immediately after recovery The residual OX19 reactions are of great value as an aid in the search for missed ambulatory patients and cases of so-called inapparent infection, but at the same time they constitute a possible source of error in diagnosis.

The suspicion arose that non specific stimulation of agglutinins, which is one of the fallacies in the serum diagnosis of the enteric fevers would interfere also with the application of the OX19 reaction. It is known that H agglutination tests are useless as a means of diagnosing enteric infection in inoculated persons because of the non specific anamnestic rise in the H titre that

may occur in the course of other febrile conditions. Great care was therefore taken to investigate the possibility of non-specific rises in the OX19 titre. Typhoid patients who gave no history of previous typhus infection but showed in their serum normal agglutinins for OX19 in titres of 1 50 or 1 100 were observed during periods of several weeks or months and no significant fluctuation in the OX19 titre could be noted Similarly patients with a definite history of a previous attack of typhus, whose serum contained residual OX19 agglutinins in titres ranging from 1 100 to 1 200 showed in no instance any evidence of non-specific re-stimulation of these agglutinins in the course of typhoid pneumonia and other febrile diseases (FELIX, 1929) It is worth mentioning that in this respect the O agglutinins for the *Proteus* X strains behave in exactly the same manner as do the O agglutinins for the typhoid paratyphoid group of organisms.

EFFECTS OF ANTI TYPHUS INOCULATION

Inoculation against louse borne typhus has been introduced during the present war in the fighting services and in civilian hospital staffs and sanitary personnel. From experiences with laboratory infections among typhus workers, and from observations under field conditions such as have been published from German sources, it would appear that inoculation with the available vaccines does not protect effectively against subsequent infection but greatly reduces the severity of the disease. It is known that the clinical diagnosis of typhus is often not altogether easy and the modified mild disease in the inoculated may be almost impossible to diagnose without the aid of laboratory methods It is therefore important to consider what effect anti-typhus inoculation has on the development of OX19 agglutinins during a subsequent attack of typhus or some other febrile disease

Vaccines made from rickettsiae of the OX19 group stimulate the formation of OX19 agglutinins in inoculated subjects. The titres are relatively low but the incidence of these inoculation agglutinins is stated by some workers to be very high for instance 57 per cent. of positive reactions have been recorded with Weigl's louse-gut vaccine, 73 per cent. with Zinsser's tissue-culture vaccine (LIU and ZIA, 1940) and nearly 100 per cent. with mouse lung vaccine (DURAND and GIROUD 1940). In comparative tests carried out in this country (FELIX, 1942) it was found that the various vaccines employed differed widely in antigenic value. One vaccine gave rise to a significant OX19 antibody response in 50 per cent. of those inoculated other vaccine groups showed considerably lower figures and one of the vaccines failed to stimulate any response at all. Table IV shows the rise and fall of these inoculation agglutinins in a group of twenty-six volunteers from whom three samples of blood were examined, one before and two after the inoculations. Thirteen persons in the group who did not show a significant rise in titre are not included in the table.

The vaccine employed in this trial may be regarded as one of the most potent types of rickettsial vaccine at present available. The table shows that the inoculation agglutinins for OX19 reached only low titres, representing a mere fraction of the maximum titres that are attained in the majority of cases of louse borne typhus.* Only two of the inoculated persons (Nos 2 and 9) had the same agglutinin levels when tested 2 weeks and again 8 weeks after the third dose all the others showed a definite drop in the titre during the

TABLE IV

SHOWING THE OX19 AGGLUTININ RESPONSE IN VOLUNTEERS INOCULATED WITH EPIDEMIC TYPHUS VACCINE. (YOLK-SAC VACCINE. BATCH C)

Case No	Agglutination of *Proteus* OX19		
	Before Inoculation	Two Weeks after Third Dose	Eight Weeks after Third Dose.
1	25−	50±	25−
2	50±	200±	200±
3	25−	100+	50±
4	*5+	100±	50±
5	50±	100±	50+
6	25−	100+	50±
7	25±	50+++	25++
8	25−	50±	25±
9	25±	50+	50+
10	25+	50+	25+±
11	25−	50++	25±
12	25±	200±	50+±
13	50+	100+±	50+±

Proteus OX19 suspension prepared at Standards Laboratory (M.R.C.) Oxford
Reading after 24 hr (2 hr incubation at 37° C and thereafter at room temperature)
+++ = strongest degree of agglutination supernatant fluid completely clear
± = weakest degree of agglutination which could be estimated with the naked eye

period of observation. It is thus seen that the OX19 antibody response to anti typhus inoculation is of a moderate degree similar to the O antibody response following T.A.B inoculation. In this respect the heat stable O antigens of typhus rickettsiae and of typhoid and paratyphoid bacilli obviously behave in the same manner and they differ profoundly from the heat labile H antigens. To the latter high titre agglutinins develop after T.A.B inoculation and do not disappear from the circulation for many months or even years.

So far hardly any observations have been recorded to indicate the behaviour of inoculation agglutinins for OX19 during subsequent febrile diseases of

* PENFOLD (1944) obtained very similar results in a group of twenty three public health workers who had been vaccinated with the same batch of vaccine.

different kinds. It seems, however logical to assume that they do not differ from residual OX19 agglutinins due to a previous attack of typhus these are known to be insusceptible to non-specific stimulation, as has been stated in the preceding section. Residual O agglutinins for typhoid and paratyphoid bacilli, whether due to previous infection or inoculation, also behave in like manner

In regard to the OX19 agglutinin curve in typhus patients who had been inoculated with rickettsial vaccines there are a few conflicting reports on record, mostly from German sources. According to SÖPPLE and FISCHER (1943), patients who were attacked with typhus after anti-typhus inoculation usually reacted to the OX19 test with lower titres than uninoculated patients. DINO (1943), on the other hand, found that 84 per cent. of his inoculated typhus patients showed, what he called, a " textbook reaction to the test and similar results had previously been recorded in cases of a second attack of typhus in laboratory workers who had a well-authenticated history of a previous attack some years before In most of these cases there was not any marked difference between the OX19 agglutinin responses during the primary and the secondary infection. If future experience confirms the observation that typhus infection in the inoculated usually runs a very mild course it seems likely that a considerable proportion of such cases will show the low titre curve of agglutinins as illustrated in Tables II and III The main point, however remains that a rising curve of OX19 agglutinins is diagnostic of typhus in the inoculated as well as in the uninoculated.

TECHNIQUE.

Most of the published data on the Weil Felix reaction are based on work carried out with fresh suspensions of living bacteria, and this technique is still in use in some countries. Suspensions of *Proteus* X19 preserved with alcohol had been suggested a long time ago (BIEN and SONNTAG 1917 BIEN 1924) but were found to be inferior to the living cultures and consequently were never used on a large scale. More recently however BRIDGES (1935) while working in the Army in India, succeeded in modifying BIEN's method and introduced preserved suspensions of the three *Proteus* OX strains which are reliable and sensitive reagents. For the past few years these standardized alcohol-treated suspensions have been in use in the Army in India and elsewhere. They are now available also through the Standards Laboratory (Medical Research Council), Oxford, and are strongly recommended for general use. It must be emphasized, however that the adoption of standard agglutinable suspensions is only the first step though a very important one, in the process of standardization of an agglutination test. The OX19 test, in common with other O agglutination tests, has not yet by any means been standardized satisfactorily and " titres " of the same sample of serum recorded by various workers may differ and in fact do differ very considerably If this is borne in mind

the reader will be less bewildered by the conflicting views that are presented to him

The macroscopic technique only should be applied in the test. Round-bottomed tubes, about 2 inches in length with an external diameter of half an inch are recommended in preference to the customary Dreyer tubes The latter are not suitable for O agglutination tests because the deposit of agglutinated bacteria cannot readily be seen at the narrow pointed end of the Dreyer tube, and it is the size and shape of the deposit that are the most important criteria in the reading of O agglutination tests

The simplest procedure is to prepare the serum dilutions in 1 ml volume and to add to each tube a single drop of the size of 0·05 ml of the concentrated standard suspension. When a patient's serum is examined for the first time the range of final dilutions tested should be 1 25 1 50 1 100 1 200 1 500 and 1 1000 or 1 20 1 40 1 80 1 160 1 320 and 1 640 Higher dilutions are added when necessary The tubes should be incubated for 2 hours at 37° C and the final reading taken after a further 22 hours at room temperature (or in the ice-chest, when working in the tropics)

Only naked-eye readings should be made at the time the final result is recorded Trace readings, which can be estimated only by means of a magnifying lens should be disregarded It is however useful to examine the tubes with a lens after they have been incubated for 2 hours, and even sooner since a high titre serum may thus be detected and valuable time gained for setting up the higher dilutions that may be required The results should be reported in actual titres obtained. Any degree of agglutination may be selected to indicate the titre provided that the accurate estimation of the particular degree of the reaction is ensured by standard conditions of the test and by the inclusion of control sera of known titres In earlier papers published by the present writer the titre was invariably indicated by partial agglutination corresponding to the sign + estimated with the naked eye. This degree of agglutination corresponds approximately to Standard in the scale employed in Dreyer's technique.

It will be noted that incubation at 37° C is recommended instead of at 50° to 52° C the temperature usually employed for incubating diagnostic O agglutination tests (GARDNER, 1929 FELIX and GARDNER, 1937) It is true that the O agglutination titres established with preserved suspensions after prolonged incubation at 50 to 52° C are usually somewhat higher than those observed after incubation at 37° C This however applies only to high titre O sera. The OX19 agglutinating serum with a titre as low as those found in a considerable proportion of typhus patients does not withstand prolonged heating at 50 to 52° C The peculiar heat lability of OX19 agglutinins in typhus sera has been discussed in an earlier paper (FELIX and OLITZKI 1929) In view of the special importance of the low titre reactions in the early diagnosis of typhus cases it is preferable to incubate the tubes at 37° C in spite of the

fact that the end titres of high titre sera may be somewhat lower than those read after incubation at 50° C

Sources of Error

One of the most important sources of error in the test is H agglutination with *Proteus* X strains, since this type of agglutination is of no significance in the diagnosis of typhus. H agglutinins due to an existing or a previous infection with *Proteus vulgaris* such as cystitis, otitis, empyema, and wound infections, are occasionally met with in the serum of healthy persons or of patients suffering from various diseases. This pitfall has been eliminated by the introduction of preserved suspensions which consist of alcohol-treated bacteria and do not or should not, contain H antigen demonstrable by the agglutination test. In two recent papers (DAMSIN and BELLINGS, 1942 SONNENSCHEIN 1943) however O agglutinins of the three *Proteus* OX types are stated to occur as a result of infection with strains of *Proteus vulgaris* possessing minor antigens of these types. SONNENSCHEIN found that sera of this kind also agglutinated *Rickettsia prowazeki* to titres similar to those for *Proteus* OX19

Another source of error may be briefly mentioned. Fresh sera of typhus patients may show a marked inhibition of agglutination over a zone of lower dilutions, usually in dilutions 1 25 and 1 50 The first appearance of agglutinins at the beginning of the disease and the low titre reactions that have been discussed before, may be entirely disguised by this phenomenon. In such cases after heating the serum for half an hour at 45° C a significant reaction may be obtained (for references see FELIX, 1930)

When examining samples of serum taken on successive occasions from the same patient it is most useful to store the remaining portion of the serum in the ice-chest and re-test it simultaneously with the subsequent specimen. This procedure is a safeguard against possible variations in the agglutinability of different batches of the preserved suspension. If a rise in agglutinin titre of at least 100 per cent. is established in this way it may be taken as indicating a significant increase in antibody content.

Interpretation of Results

From what has been stated in the preceding sections it is evident that the most important diagnostic criterion is the rise in OX19 titre during the attack and its fall during convalescence. When diagnostic conclusions are drawn from the result of a single agglutination test, complete agglutination of the standard suspension at 1 80 or 1 100 may be considered as significant, provided the patient has not been recently inoculated with typhus vaccine and is not a native of an endemic area. This degree of agglutination corresponds to Total in the scale employed in Dreyer's technique. If the patient has a history of inoculation with a rickettsial vaccine 2 or 3 months before the onset of his illness complete agglutination in 1 200 or over may be taken as strongly

suggestive of active infection. In endemic areas even higher titres may occasionally be found to be due to past infection A marked increase in titre, however established by repeated examinations at intervals of 2 days is generally conclusive. Quite often the increase may be observed even after an interval of 24 hours

On the other hand, an unaltered titre of agglutination, if established by repeated examinations throughout the whole course of an acute disease, will reveal the non specific or residual character of the reaction. This finding may as a rule be interpreted as serological evidence against the typhus nature of an existing fever because complete absence of rise and fall in the OX19 titre is quite exceptional in louse-borne typhus and occurs only in cases of extreme severity which usually end fatally For this reason diagnostic significance can be ascribed to the negative as well as to the positive result of the test.

Although complete (Total) agglutinations in dilutions 1 25 and 1 50 are not decisive when obtained in the first examination of a patient s serum, still, they ought not to be ignored in routine work. When found in a second or third examination in the course of the disease after an earlier negative result, these low titre reactions are as decisive as those obtained in high titres The low titre reactions are of especial importance in the early diagnosis of cases and have been employed almost universally ever since the test was first introduced In recent papers published in this country and abroad the suggestion has been made that for practical purposes of typhus diagnosis any positive reading below the serum dilution 1 100 may be ignored and regarded as normal (VAN ROOYEN and BEARCROFT 1943) There is no reason whatever for this suggestion. The occurrence of low titre normal agglutinins in dilutions up to 1 100 was well known to the early workers, but the means of differentiating these reactions from the specific responses in typhus fever was also known (WEIL and FELIX 1918) Table III shows that in a certain proportion of cases the maximum titre may never exceed or even reach the level of 1 100 If the dilutions 1 25 and 1 50 are not included in the routine test such cases are missed, and in other instances the serological confirmation of the diagnosis is unduly delayed. Most of the statements regarding the relatively late appearance of a positive OX19 reaction and the slight assistance derived from it in the early diagnosis of cases of louse borne typhus are obviously due to failure to pay attention to low titre reactions.

In endemic areas it is often of great importance to discover whether an earlier illness was typhus or not, and the OX19 reaction is employed for the retrospective diagnosis of missed cases especially the mild and atypical cases that occur quite often in adults and more often still in children It is seen from the examples given in Tables II and III that the majority of cases of louse-borne typhus show a high OX19 titre during the early weeks of convalescence and that a significant drop in titre may be demonstrated at that time by suitably spaced repeat examinations After some months however

the fall in titre is no longer steep enough to be readily demonstrable. Those cases which showed a low titre OX19 reaction during the attack cannot be detected by the test after they have recovered.

The OX19 reaction is also positive in cases of so-called inapparent infection which show no clinical symptoms whatever. Such cases are of especial epidemiological importance in countries where typhus is endemic. The diagnosis of these symptomless infections is based on the demonstration of a rising or falling OX19 titre.

SLIDE AGGLUTINATION TESTS.

A rapid slide test for carrying out the OX19 reaction was recommended by WELCH (1937) in the U.S.A. and by CASTANEDA *et al.* (1940) in Mexico. German workers have been employing this method extensively since the beginning of the present war and have published a great number of reports describing various modifications of the technique. The aim of all these modifications is to enable the test to be carried out under the most primitive field conditions, when no laboratory or even hospital facilities are available. Preserved suspensions of *Proteus* OX19 are distributed from central laboratories and the test is carried out by mixing a drop of finger blood, or of the separated serum with a drop of the concentrated suspension. Some of the German military laboratories issue the OX19 antigen in the form of an alcoholized or formolized suspension stained with methylene blue; others send out slides on which a number of drops of the concentrated suspension has been dried. Dried cultures of *Proteus* OX19 reduced to a fine powder are also employed. Another procedure is to collect the specimens on glass slides in the form of dry smears of whole blood and test subsequently by adding a drop of the antigen. The tests are read with the naked eye according to the intensity and rapidity of clumping and it is stated that the results compare favourably with those obtained with test tube agglutination.

The slide tests are employed in epidemiological surveys of large communities, and mild cases and "inapparent" infections may be detected by this means. The test is also used in rapid bedside diagnosis in field conditions. Some of the German workers accept the results of slide agglutination as final, while others employ the test as a preliminary to the customary tube test. Since the original papers on the subject are not readily accessible at the present time, the reader may be referred to a number of abstracts written by Sir JOHN MEGAW in the *Tropical Diseases Bulletin* Vol. 39 (1942), pp. 372 and 811 and Vol. 40 (1943), pp. 153, 529, 588 and 800. These simple tests seem to be very useful under the exceptional conditions which called for the adoption of the various procedures.

MURINE TYPHUS. TYPE OX19

Murine typhus, often but inappropriately called endemic typhus, has a world wide distribution, and our fighting forces are likely to make contact

with the disease in the Mediterranean, the Middle East and the tropical and subtropical Far East (see Table I) This variety of typhus is transmitted to man by the rat flea and usually causes only sporadic cases, although outbreaks may occur when rat infestation is exceptionally heavy The disease runs a mild clinical course with a very low case fatality rate and does not, therefore constitute a serious menace The agglutination reaction with *Proteus* OX19 is found in murine typhus with the same frequency as in louse borne typhus that is in almost every case and the two varieties of the disease can be differentiated serologically only by complement fixation or agglutination tests with rickettsial antigens (BENGTSON and TOPPING 1942 PLOTZ 1943 VAN ROOYEN and BEARCROFT 1943 STUART-HARRIS RETTIE and OLIVER, 1943)

The statement is often made that the OX19 reaction is not as early a sign in murine typhus as it is in the louse-borne variety It is however obvious from the published data that there has been little occasion for studying the development of agglutinins in the early stages of murine infections The sporadic cases do not often come under observation early enough for adequate tests to be carried out in the manner illustrated in Tables II and III So far nearly all the workers with the exception of REITLER *et al.* (1939) have failed to pay attention to the two types of the agglutinin curve referred to in connection with louse-borne typhus. Such incomplete data as are found scattered throughout the extensive literature on murine typhus do however indicate that the two types of antibody response occur in cases of murine typhus, and that the maximum titres are attained approximately at the time of defervescence SPARROW and MARESCHAL (1940), who transmitted the disease experimentally to mental patients with a view to the production of therapeutic effects made very careful observations on the agglutinin curves in seven patients and found a significant rise in the OX19 titre as early as in cases of louse borne typhus

Accidental infection in a number of laboratory workers in this country recently provided an opportunity for testing the question of the alleged late appearance of OX19 agglutinins in murine typhus. VAN DEN ENDE *et al* (1943) published a detailed account of these laboratory infections, including the results of OX19 tests, and concluded (page 330) Agglutinins either did not appear or did not increase in amount before the second week of the disease
My own experience with tests carried out on some of these cases proved to be different. Five of the twelve patients in the series published by VAN DEN ENDE *et al* were examined according to the technique discussed in the present paper and the results obtained in four of the cases are shown in Table V The fifth case (Y) was ambulant throughout, had no febrile symptoms, and is therefore not included in the table.

These four workers had received several courses of typhus vaccine including a murine vaccine but failed to show any OX19 agglutinin response. During the illness however all of them gave a significant OX19 reaction which,

as Table V shows, was demonstrable in three of the four cases well before the end of the first week. In fact, even the figures published by VAN DEN ENDE *et al.* which were obtained by the use of a different but unspecified technique,

TABLE V

SHOWING *Proteus* OX19 AGGLUTINATION TITRES IN FOUR CASES OF LABORATORY INFECTION WITH MURINE TYPHUS.

Name	Date	Day of Illness.	Agglutination of *Proteus* OX19 Suspension (Standards Laboratory Oxford).	Significant Rise of Titre first Observed on
A	9.10.41—before inoculation		50±	
	6.11.41—14 days after 3rd dose of yolk-sac vaccine Batch A (epidemic)		50±	
	8.12.41—16 days after 3rd dose of rat-lung vaccine, Batch E (murine)		50±	
	13.1.42—14 days after 3rd dose of yolk-sac vaccine, Batch C (epidemic)		50±	
	17.1.42	2	50±	
	19.1.42	4	50±	
	21.1.42	6	100±	6th day of illness
	26.1.42	11	1 000+	
E	9.10.41—before inoculation		25−	
	6.11.41 }		25−	
	8.12.41 } inoculated as A		25−	
	12. 1.42. }		25−	
	20.1.42	3	25−	
	21.1.42	4	25−	
	23.1.42	6	25−	
	26.1.42	9	25++	9th day of illness
	29.1.42	12	50+	
	6.2.42	20	100±	
	9.2.42	23	50+	
	17.2.42	31	50+	
J	9.10.41—before inoculation		25 tr	
	6.11.41 }		25 tr	
	8.12.41 } inoculated as A		25 tr	
	13. 1.42 }		25 tr	
	17.1.42	3	25 tr	
	19.1.42	5	50+	5th day of illness
	21.1.42	7	200±	
	26.1.42	12	400±	
L	15.11.41—before inoculation		50 tr	
	8.12.41—14 days after 3rd dose of rat-lung vaccine, Batch E (murine)		50 tr	
	27.1.42—21 days after 3rd dose of yolk-sac vaccine, Batch C (epidemic)		50 tr	
	1.2.42	1	50±	
	5.2.42	5	100+	5th day of evening pyrexia (ambulant case)
	8.2.42	8	200±	

tr. = trace agglutination, visible by means of magnifying lens.

do not justify their conclusion, since four of the six cases that are listed in their Table I showed an increase in titre on or before the 7th day and the remaining two cases were not examined at the right time intervals to show that there was no significant rise before the end of the first week.

The conclusion, therefore seems justified that many cases of murine typhus can be diagnosed by the OX19 test during the first week of illness provided the tests are carried out and interpreted in the manner already discussed in this paper

Tick borne Typhus Serological Type Undetermined

(*a*) fièvre boutonneuse.

This variety of typhus is found in all the countries along the European and African shores of the Mediterranean, and in the Balkans including Rumania The disease is transmitted to man by the dog tick *Rhipicephalus sanguineus* and is one of the mildest forms of typhus with almost no mortality Unlike louse-borne and murine typhus cases of fièvre boutonneuse give irregular results in agglutination tests with the *Proteus* OX antigens A significant reaction usually appears very late in the disease and the maximum titres reached are markedly lower than those in louse borne and murine typhus The serum of some patients with fièvre boutonneuse reacts only with *Proteus* OX2, or shows a higher agglutinin titre for OX2 than for OX19 (Durand 1932 Felix, 1933b) Either of these results may as a rule be interpreted as confirming the diagnosis of fièvre boutonneuse and also as excluding that of louse borne or murine typhus When, on the other hand, the predominant agglutinins are of the OX19 type a differential diagnosis cannot be made. Tests with rickettsial suspensions have not yet been reported in cases of fièvre boutonneuse.

Durand (1932) very carefully investigated the course of the formation of *Proteus* OX agglutinins in a series of mental patients who were receiving fever therapy by means of induced fièvre boutonneuse. In the majority of his patients the maximum titres for either OX19 or OX2 were observed during the first 2 weeks after the defervescence in some cases the maximum titres were not attained until the 4th or 5th week of convalescence According to the accepted criteria these late irregular and low titre agglutinins have been classed as group agglutinins due to minor or group antigens present in the rickettsiae of fièvre boutonneuse, whereas the OX19 agglutinins in louse borne and murine typhus are due to a major antigenic component of the corresponding rickettsiae (Felix, 1933b)

(*b*) tick borne typhus of india

A tick borne typhus-like fever was first described from India by Megaw (1917 1921) and some of the more recent observations have been analyzed in a careful study by Bord (1935) So far the epidemiology of the disease

and the behaviour of the causal rickettsiae in experimental animals have not been investigated. Consequently the type or types of agglutinin response to the *Proteus* OX antigens have not yet been established in cases of tick borne typhus in India. By analogy with what is known from the work on Rocky Mountain spotted fever (SPENCER and MAXCY 1930 DAVIS and PARKER, 1933) on the tick bite fever of South Africa (PIJPER and DAU 1930 1931 1932) and on fièvre boutonneuse, it may be assumed that both the OXL9 and the OX2 antigens are of equal importance in the diagnosis of the Indian variety of the disease. Whereas only these two antigens need be employed in routine work in the Mediterranean theatre of war in India the OXK antigen is also required, since cases of the OXK type of typhus have been reported from many parts of the country (MACNAMARA, 1935 BOYD 1935)

SCRUB TYPHUS (TSUTSUGAMUSHI) TYPE OXK.

Scrub typhus or tsutsugamushi is one of the major dangers to the fighting forces in the Far East. Since the OXK type of typhus was first identified in the Federated Malay States by FLETCHER and LESLIE (1925), it has been found that the disease is endemic in nearly all the tropical countries of the Far East (see Table I) The vectors are larval mites (Trombiculae) and the reservoirs of the infection are rats and field mice The severity of the disease varies greatly in different localities and the case mortality is stated to vary from 1 per cent. to 60 per cent. A useful account of the clinical and epidemiological aspects of the disease has been published by LEWTHWAITE and SAVOOR (*Lancet* 1940).

Of the three *Proteus* OX strains only the OXK is agglutinated in cases of scrub typhus Thus the test is not complicated by any group reaction to the OXL9 and OX2 antigens. Nevertheless the technique and interpretation of the OXK reaction is fraught with difficulties which may be summarized as follows

(1) Suspensions of *Proteus* OXK, whether live or preserved, are more susceptible to non-specific "normal" agglutination by sera from man and experimental animals than are suspensions of OXL9 and OX2 (FELIX, 1933a) The minimum titre of a "significant" reaction with OXK should, therefore, be double the titre required in OXL9 or OXL2 agglutination. That is to say when a patient's serum is examined for the first time complete ("total") agglutination at 1 160 or 1 200 may be taken as diagnostic of an active infection.

(2) It is more difficult to make a sensitive and stable suspension of the OXK strain than of the strains OX19 and OXL2 (MARTIN 1931 BRIDGES, 1944). Alcohol treated suspensions of OXK often show a certain degree of granularity and thus tends to increase on storage. Non-specific agglutination of such suspensions may readily be obtained with relatively high dilutions of serum from patients who are suffering from various febrile diseases. The high-titre OXK reactions observed by VAN ROOYEN and BEARCROFT (1943) in a number of their cases of louse-borne and murine typhus were most likely

due to this source of error In another paper recently published from the Middle East (BROCKBANK and WHITTAKER, 1944) it is stated that agglutination against *Proteus* OXK was not performed because the suspension of the strain was unreliable. Special precautions should therefore, be taken to guard against this pitfall. The time of expiry of the OXK suspension should be made shorter than that of the OX19 and OX2 suspensions, and the quality of each batch should be carefully checked by the inclusion of adequate controls in the tests.

(3) The OXK reaction is found positive in almost every case of scrub typhus if the serum is tested several times during the fever and early convalescence. In this respect the OXK reaction holds the same position in scrub typhus as the OX19 reaction does in louse borne and murine typhus The maximum titres for OXK in cases of scrub typhus are also often as high as those for OX19 in the appropriate varieties of the disease, provided that a sensitive OXK suspension is available. There is, however a serious drawback to the OXK test, which is caused by the relatively late appearance of OXK agglutinins Those who have had the greatest experience of scrub typhus in Malaya (FLETCHER and LESSLAR, 1926 LEWTHWAITE and SAVOOR 1940) and in Sumatra (WOLFF 1932) agree that a significant reaction is rarely observed before the second week of the disease and that the maximum titres are usually reached in the 3rd or 4th week. Thus the test is not an aid to early diagnosis It should be noted, however that an earlier appearance of OXK agglutinins has been reported in cases of scrub typhus in India (MACNAMARA, 1935 BOYD 1935) The workers in India employed preserved suspensions which had been prepared by BRIDGES (1935)

The technical details that have been discussed in connection with the OX19 reaction apply also to the OXK test. A rise in titre of at least 100 per cent when established with a properly checked suspension may be considered as a significant reaction. If repeat specimens are examined at intervals of not more than 2 days it may be possible to confirm the diagnosis at a somewhat earlier stage during the disease. The agglutinin response in cases of scrub typhus has not yet been studied with sufficient precision to give an adequate answer to the question whether a relationship exists between reaction curve and clinical course similar to that which obtains in louse borne typhus In studies of this kind special attention should be paid to what has been called the low titre reaction curve.

SUMMARY

Two different types of the curve of OX19 agglutinin formation are found in patients suffering from louse borne typhus. The two types of reaction curve are related to the clinical course of the disease and form the basis for the interpretation of the results of the Weil Felix test.

Rickettsial vaccines stimulate demonstrable OX19 agglutinins in a relatively high proportion of inoculated persons. The OX19 antibody response is of a moderate degree, similar to the O antibody response after T.A.B inoculation.

Residual OX19 agglutinins, due to a previous attack of louse-borne typhus, do not show significant fluctuation of the titre in the course of various febrile diseases. It may be assumed that the same holds for OX19 agglutinins produced in response to anti-typhus inoculation. Residual O agglutinins for typhoid and paratyphoid bacilli, whether due to previous infection or inoculation, also behave in like manner.

The technique of the agglutination test with preserved suspensions of *Proteus* OX19 is described. Repeated tests with low dilutions of serum, including dilutions 1 25 and 1 50 are of especial importance in early diagnosis. Some of the possible sources of error are discussed.

The various modifications of a slide agglutination test, now used by German workers for rapid diagnosis in field conditions, are briefly mentioned.

The following typhus-like fevers occur in the areas which at present are, or soon may become a theatre of operations, viz., murine typhus, "fièvre boutonneuse," tick typhus of India and scrub typhus. The *Proteus* OX reactions peculiar to each of these varieties of the disease are compared with the OX19 reaction as it is known in louse borne typhus.

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NOTE ON THE PREPARATION OF SUSPENSIONS FOR THE WEIL-FELIX TEST

BY

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In a paper published some years ago* I described the details of the technique used in the preparation of alcoholized suspensions of the three *Proteus* OX strains that are employed in the Weil-Felix test. Certain changes in technique have been adopted subsequently and it may be useful to other workers to give a brief description of the procedure now followed in this laboratory

Plate the *Proteus* OX culture to be used on plain agar If the culture contains organisms of the spreading H+O form plate on phenol-agar (1 in 1,500) to ensure growth in single colonies Incubate for 24 hours Pick a number of colonies, say six, each on to two agar slopes and incubate 24 hours. The one slope is used for test, the other is kept as "office copy"

Add about 2 ml. of saline to each test slope and wash off the growth. Pour off the suspensions into clean test tubes and fill the tubes about three quarters full with 96 per cent. alcohol. Shake up all tubes thoroughly during the course of 1 hour Remove the alcohol in the centrifuge and resuspend the organisms in 0·25 per cent. formol-saline. Reduce to suitable density for agglutination test.

Test all suspensions with the corresponding type serum and choose that which agglutinates most rapidly most completely and to the highest titre The test is preferably carried out with typhus serum, if available, rather than with *Proteus* rabbit immune serum.

If the original culture is known to be in good condition the whole of the above may be omitted, and the suspension prepared from the whole culture. But occasional colony selection is advisable.

Growth in bulk is carried out in Roux bottles or screw-capped "medical flats," which have been coated on one side with unfiltered agar One broth tube (5 ml.) is inoculated from the office copy of the selected colony for each Roux bottle to be used. The broth tubes are incubated for 24 hours after which the contents are poured into the Roux bottles. The broth is allowed to flow over the whole surface of the agar and the bottles are then placed in the incubator with their necks slightly raised so that the broth remains at one end.

After 24 hours incubation add a small quantity of saline to each bottle and wash off the growth. Filter through cotton wool into one or more screw

*Bridges, R. F (1935) *J. R. Army med. Cps.*, 64 153

capped bottles. Add 96 per cent. alcohol in the proportion of not less than 4 volumes to 1 volume of suspension. Shake up thoroughly during the course of 1 hour

Suck off as much as possible of the supernatant alcohol and transfer the remainder containing the organisms to centrifuge tubes. Swing rapidly for a few minutes. Pour off the alcohol from the deposited organisms, removing the last drops with a pipette.

Resuspend the organisms in sterile saline solution and transfer to screw capped bottles. Shake up very thoroughly until it is seen that all clumps have been smoothed out and no granularity remains. Add 2 per cent buffered formol-saline to make concentration of formalin 0·25 per cent. (*i.e.*, add one-seventh of the volume of suspension).

In the case of the OXK strain the alcoholized organisms should be resuspended in sterile distilled water *not saline* and all further dilution should be made with distilled water But the 2 per cent. formalin may be added in the form of buffered formol-saline as in the case of the OX19 and OX2 strains.

Standardize the suspension by adding more sterile saline (distilled water in the case of OXK) and 2 per cent. buffered formol-saline (final concentration of formalin 0·25 per cent) to a density equivalent to 4,500 million *Bacterium coli* per ml.

Note 1 2 per cent buffered formol-saline is prepared by adding the required quantity of formalin to a measured quantity of sterile saline and then bringing the pH to 7·6 by addition of Na_2HPO

Note 2 In the Standards Laboratory we carry out the standardization of the suspension by means of an electric absorptiometer But if Brown's tubes are used the following is a simple method —

Use only tube 3 since this is more easily matched than any other One volume of suspension is diluted with volumes of saline until it is found to match tube 3 Then the amount of fluid which must be added to bring to the required density is equal to $\frac{(a-3\cdot7)x}{3\cdot7}$ where "a" is the number of *times* that the suspension must be diluted to bring to the value of tube 3 and "x" is the volume of suspension to be diluted Thus, supposing we have 50 ml. of suspension and it is found that it must be diluted with 11 volumes of saline, or twelve times, to bring it to the density of tube 3 then the quantity of fluid which must be added to give a concentration equivalent to 4,500 million *Bact coli* per ml is equal to $\frac{(12-3\cdot7)50}{3\cdot7} = 112$ ml Thus fluid is added as to seven-eighths in the form of sterile saline (distilled water in the case of OXK) and one-eighth of buffered formol-saline.

The figure 3·7 in both numerator and denominator of the above formula represents the number of times that the finished suspension is required to be denser than tube 3 It can be increased or diminished according as a stronger or weaker suspension is thought desirable

CORRESPONDENCE

THE TREATMENT OF TROPICAL ULCERS AND OTHER SKIN AFFECTIONS WITH LOCALLY PREPARED ACRIFLAVIN-KAOLIN POWDER.

To the Editor TRANSACTIONS *of the Royal Society of Tropical Medicine and Hygiene*

SIR,

The necessary conservation of drugs such as zinc oxide, iodoform, bismuth, and liquid paraffin for the compounding of Z I.P and B I.P , led me to exploit less costly and more easily obtainable material

For the past 6 months at the Karonga hospital I have used, exclusively and with good results, a preparation, A.K. powder made from a local kaolinitic earth impregnated with acriflavin in the treatment of tropical and other, ulcers and all skin affections which require an antiseptic emollient drying powder

The crude masses of gritty earth are pounded in an African wooden mortar put in a 12-gallon drum, and thoroughly stirred up in water The washing may have to be repeated to recover the bulk of the clay The supernatant fluid, containing the particles in suspension, is poured off into another receptacle, and in a few hours an almost impalpable white clay is deposited, which is collected and fire-dried, and the hard cake thus obtained ground into powder

Two soluble tablets 1 75 grains each, of acriflavin, dissolved in half a pint of water are mixed with half a pound of the powdered earth, which is again fire-dried and pulverized when a fine sterile ochre-coloured product is obtained. In this district, 50 pounds of crude earth yield 4 of fine powder

On reception the ulcer is irrigated with warm 1–1000 pot. permanganate lotion and the A.K. powder dusted on with a dredger A suitable piece of lint, wrung out in sterilized ground nut oil is superimposed and a bandage applied.

The irrigation and dressing is repeated every other day

Patients express immediate relief from pain and discomfort on completion of the dressing

Foul tropical ulcers are particularly benefited and clean up rapidly The effect on chronic ulcers such as veld sores is striking

When definite signs of healing appear the treatment described is discontinued, and ointments, equal parts of boric and zinc oxide, later zinc oxide alone, are used to finish off with. Syphilitic and yaws ulcers, of course, require constitutional treatment as well.

Half a pound of the A.K. powder suffices for an average of thirty cases, and the saving in time and expense is considerable.

The method is simple and effective and has been introduced at the rural dispensaries in the district.

I have entered into some detail in order to save others similarly situated the trouble of experiment.

I am etc.

J O Shircore.

Karonga,
Nyasaland.

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TRANSACTIONS
OF THE
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

VOL. XXXVII No 6 MAY, 1944

ORDINARY MEETING
of the Society held at
Manson House, 26, Portland Place, London, W,
on
Thursday, 16th March, 1944, at 8 p.m
THE PRESIDENT
SIR HAROLD SCOTT K.C.M.G M.D F.R.C.P
in the Chair

PAPER

HEAT EFFECTS IN BRITISH SERVICE PERSONNEL IN IRAQ

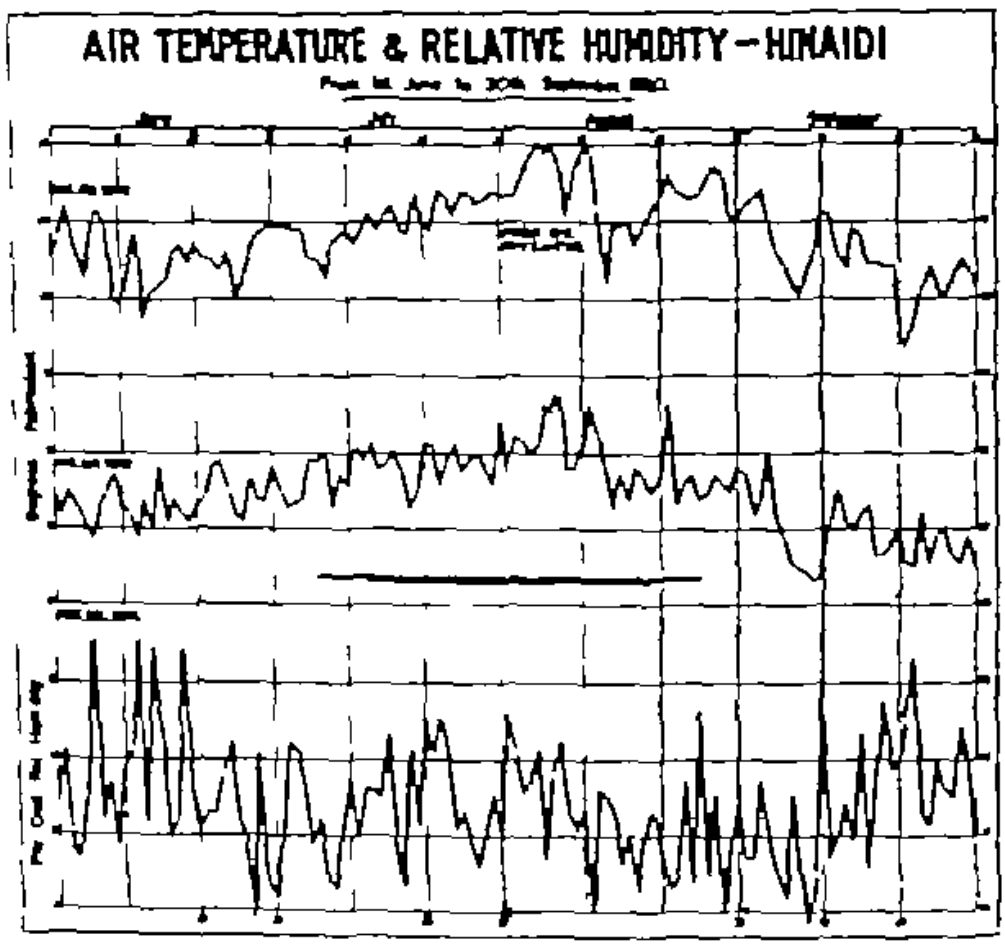
BY
T C. MORTON O.B.E. M.D. F.R.C.P Air Commodore, R.A.F
Institute of Pathology and Tropical Medicine R.A.F

CLIMATOLOGY

Iraq was aptly described by a British Tommy in the last war As a country consisting of two ruddy long rivers and miles and miles and miles of sweet damn all. Apart from a thin fringe of cultivation bordering the rivers and canals at few places more than a mile in width, the country consists of flat desert in the summer and weary miles of flooded countryside in March and April. In the winter the ubiquitous camel thorn and stunted desert shrubs veil the desert with a thin mantle of green and afford pasturage to the numerous camels goats and fat-tailed sheep of the nomad and semi nomadic tribes. The desert

does not consist of sand but of alluvial mud deposited by the floods The prevailing tone is a drab khaki which reflects and radiates the burning rays of the sun and thus panorama is varied only by salt pans in the low lying depressions. Southern Iraq is in reality a flat delta In Biblical times the two rivers, the Tigris and Euphrates, had separate mouths and the alluvial deposits carried down by them in the course of centuries have gradually built up the delta, causing it to encroach on the Persian Gulf to such an extent that Ur of the Chaldees, once a flourishing sea port of Sumeria, is now some 160 miles inland.

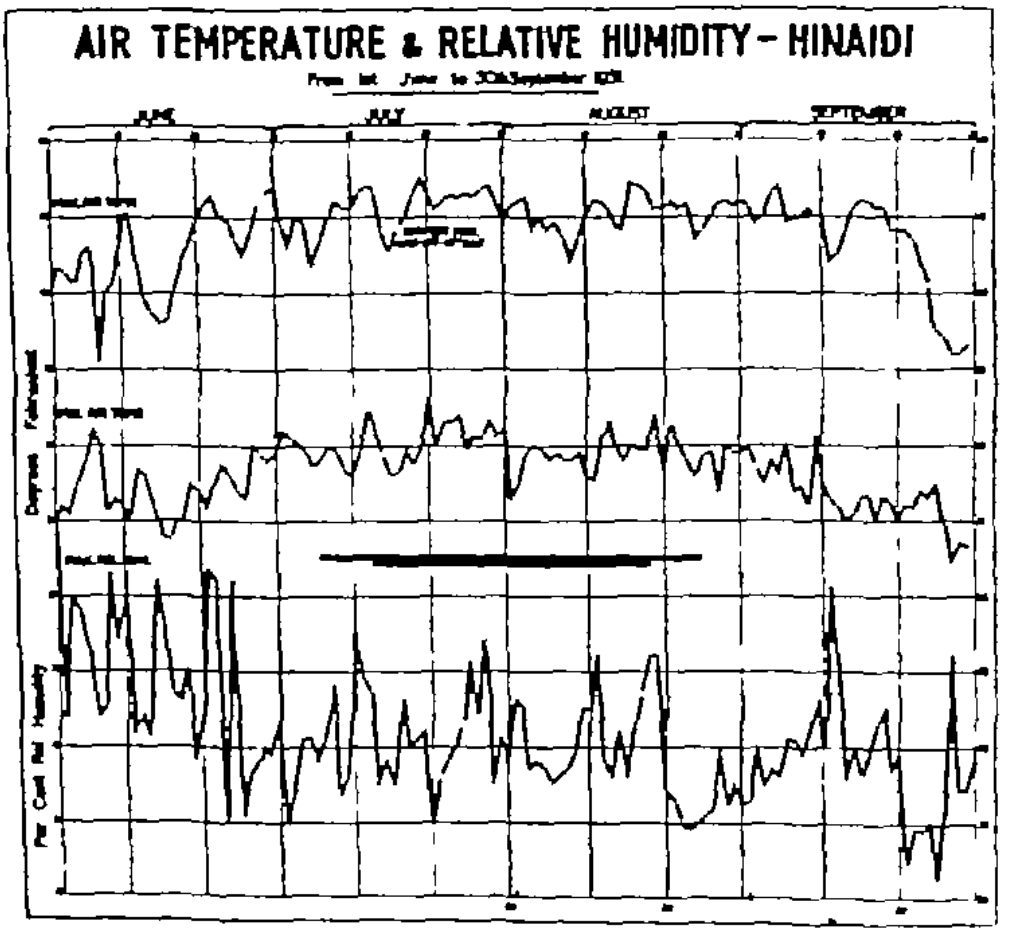
GRAPH 1



The main annual rainfall of Iraq is only 6 inches a year and is limited to 4 months from November to February The hot season commences in May and continues until the end of September the last fortnight in July and the first fortnight of August being the hottest time of the year The highest shade temperature for the last 15 years, as far as R.A.F meteorological data record, was a temperature of 125 F at Mosul in northern Iraq Fortunately the nights are relatively cool, the highest night temperature recorded during the 1930 heat wave was 88° F with a humidity of 42 per cent. on a day when the

shade temperature reached 123° F The relatively cool nights even in the hottest months render Iraq a possible country for the white man living under good conditions, though day temperatures of 135° to 140 F are not uncommon in Double Fly E.P tents. A study of annual meteorological charts shows that severe heat waves tend to occur about every third year when for from 3 to 5 days the maximum temperature remains in the 120°s and, as Sir WILLIAM WILLCOX (1920) recorded, it is the cumulative effects of heat that matter the greatest incidence of cases occurs on the third or fourth day of the heat wave and

GRAPH 2



the individual frequently succumbs to heat effects in the night or early morning when the atmospheric temperature has fallen very considerably

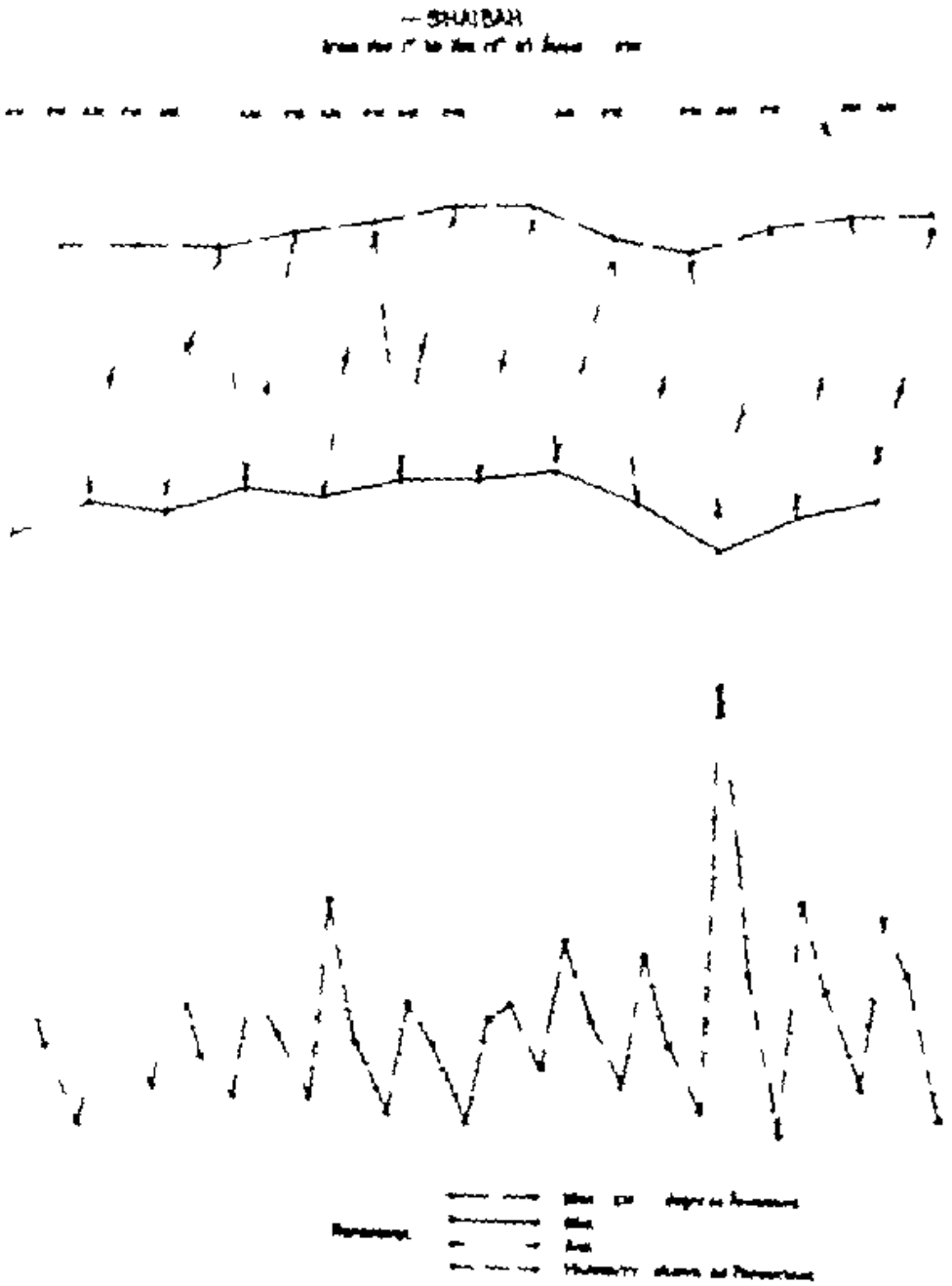
AETIOLOGY

Heat hyperpyrexia and heat exhaustion are due to a general parboiling or overheating of the blood and body tissues and not to any mysterious property in the rays of the sun in the tropics. The clinical syndromes resulting from overheating are by no means confined to the tropics. They occur in furnace

workers in temperate climates but owing to the men working in short shifts and then being removed to a cooler atmosphere the profound changes seen in endemic areas rarely occur as the break and return to a cooler atmosphere gives the body a chance to overcome the results of dehydration Active service conditions

GRAPH 3

MAXIMUM AND MINIMUM DAILY TEMPERATURE AND CORRESPONDING HUMIDITY

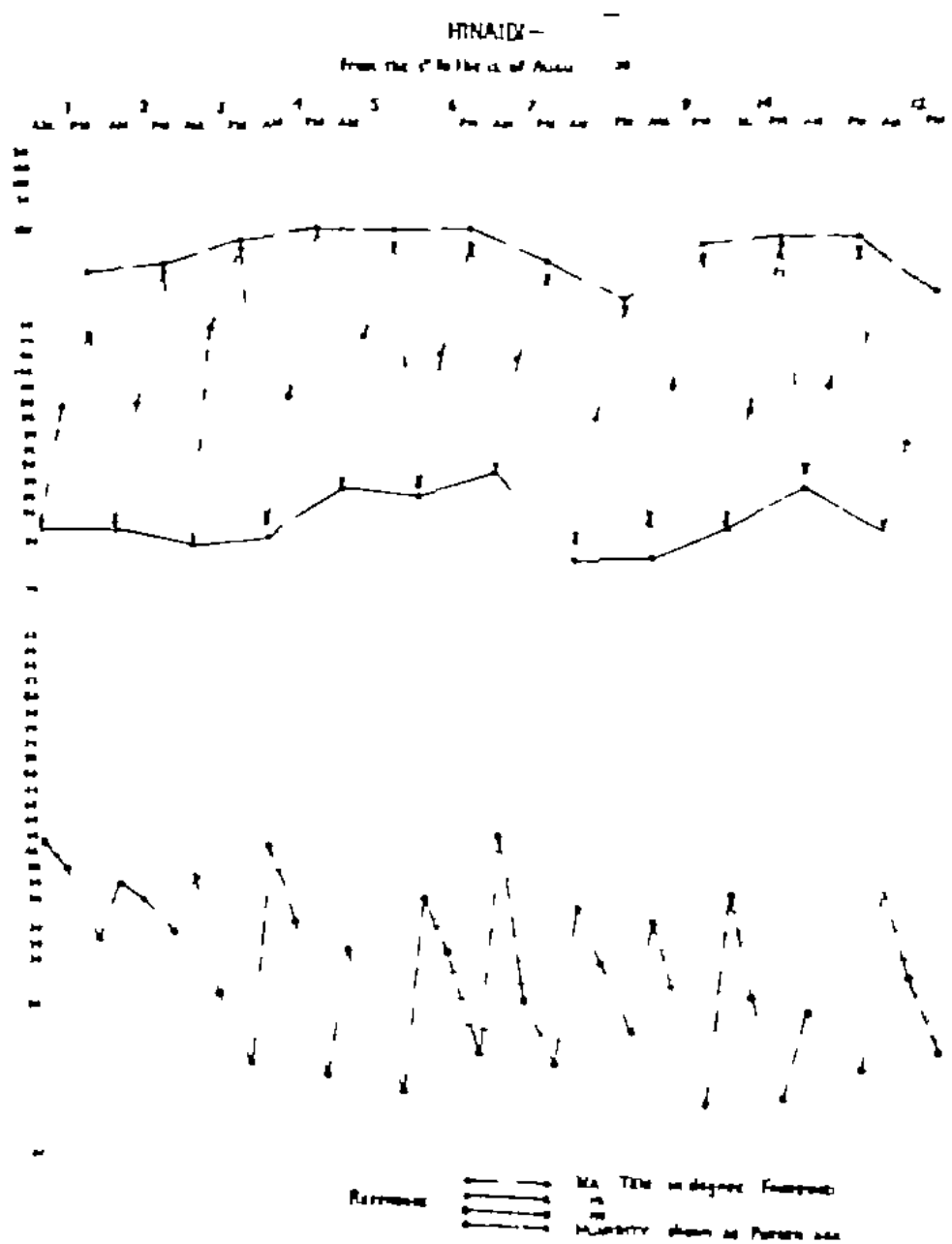


in countries such as Iraq especially when unsalted new reinforcements from temperate climates arrive in the middle of the hot weather always lead to an increased incidence of cases. Meteorological factors such as humidity play an important part as regards the suppression of sweating and the heat hyperpyrexia

syndrome will always be common in hot, humid areas such as Basrah, whilst heat cramps are more common in hot dry areas. The overheating of the body throws a strain on the heat regulating system and the heat loss occurs mainly through the sweat glands. It is interesting to note that it has been proved

GRAPH 4

MAXIMUM AND MINIMUM DAILY TEMPERATURE AND CORRESPONDING HUMIDITY



that more sodium chloride is lost in the sweat of new arrivals to the tropics than in the acclimatized, and recent experience has shown how important a role sodium chloride plays in the genesis of heat exhaustion and heat hyperpyrexia. It has been known for many years that the muscular cramps that stokers suffered

from could be prevented by the addition of salt to their drinking water but it is only within comparatively recent years that this observation has been applied to the tropics and the paramount importance of a sufficiency of salt and water for the maintenance of health been realized. Army experiments were carried out in India in 1938 and it was found that after a normal route march of 9 miles in the hot weather with a shade temperature of 104·3° F and a relative humidity of 47 per cent. that the average salt loss (NaCl) per man was 6·8 grammes and that the water loss amounted to between 6 and 8 pints, in addition Lendon (1939) found in a 9 mile march at 107° F the loss during the march was 6·5 grammes of NaCl the blood chloride level being reduced from 500 mg. to 417 mg per cent. In order to maintain efficiency in the tropics in the hot weather it is necessary to ingest about ½ to 1 oz. of salt a day normally the food contains half this amount so that the balance must be made good by extra salt. Ten grains of salt to a pint of cold water makes quite a palatable drink and considerable quantities of salt can be added to fresh or tinned tomato juice flavoured with a little Worcester sauce, which makes an appetising non-alcoholic cocktail before lunch. The universal popularity of well-salted almonds, pistachio nuts and chip potatoes etc in the tropics is a physiological craving that should be encouraged and made available to all ranks by being offered for sale at the wet canteens sergeants and officers messes, etc. The fluid loss should be made good and, dependent on the amount of sweating and nature of the work involved the water intake required will vary from 1 to 2 gallons per man per day In workshops the following drink* should be readily available and men should be instructed to drink frequently but not more than 8 ounces at a time

Sodium chloride	6 ounces	Seventeen fluid ounces of this con-
Potassium	4 ounces	centrated solution to be added to 3
Water	1½ pints.	gallons of water for drinking a flavouring agent may be added.

Biochemistry in Heat Effects

The whole subject is in a condition of flux. The physiologists in the laboratory have attempted to over simplify the matter by such extreme subdivision that they have produced a classification of subclinical entities that is of little value to the clinician whose sole object is to make a correct diagnosis and institute the appropriate treatment. This problem awaits solution in spite of all the careful experimental work of Dr Frank Marsh (1930) of the A.I.O.C., where the preventive measures adopted by that far-seeing company have been so successful that he is starved for human clinical material. I was delighted to hear that the War Office and Medical Research Council sent two investigators

* For this I am indebted to Dunlop McNee and Davidson's *Text Book of Medical Treatment*

out to Iraq in 1943 and we await their report with great interest. My own attempts in this field were limited to chloride investigation of the urine and blood urea estimations I found the urinary chlorides markedly reduced in all severe cases of heat exhaustion and in every case of heat hyperpyrexia The blood urea was raised in one or two cases of prolonged heat hyperpyrexia but I could find no evidence of permanent renal damage due to heat effects *per se* The critical assessment of electrolytic imbalance, whether alkalosis or acidosis is predominant in a particular case at a particular moment, is a matter for the biochemist but what the clinician wants is a method of treatment which will safely restore the disordered metabolism A treatment which is too specific, for example alkalies to treat acidosis or ammonium chloride for alkalosis, is too dangerous unless the services of a well-equipped laboratory are at hand, for one has learnt by experience how easy it is to swing from one extreme to another especially when the intravenous route is necessary Fortunately in 0·9 per cent. NaCl and 5 per cent. glucose we have a safe and reliable therapeutic treatment readily available which if administered early will restore the disordered metabolism Even in these days of facile intravenous therapy it is necessary to stress that even these simple solutions must be carefully administered and the intake and output charted if pulmonary oedema is to be avoided

Nomenclature.

There are three distinct clinical entities although the dividing line between them is not absolute and borderline cases may occur

1 *Syncope*

This occurs in temperate climates in hot stuffy atmospheres and also in heavily overladen soldiers on the march The essential pathology is a temporary cardio-vascular collapse which, like other faints, may progress to marked prostation with giddiness, a small soft fluttering pulse shallow breathing, dilated pupils a cold skin and subnormal temperature. On recovery the patient is bathed with a cold clammy sweat and severe headache and mental confusion may follow for a few hours Death may occur in cases with heart disease The urinary chlorides are not reduced.

Treatment—Dorsal decubitus in a cool place, the loosening of tight clothing and the bathing of the face with cold water together with the application of ammonia to the nostrils and a small dose of sal volatile

2. *Heat exhaustion*

This is a clinical syndrome tending to occur as a result of severe and usually prolonged exposure to high atmospheric temperatures and is characterized by collapse, profuse perspiration, low blood pressure, nausea and vomiting and in severe cases muscular cramps the urine is invariably

diminished and chlorides both in the blood and urine are markedly reduced. The blood pressure is invariably low The mouth temperature may be normal or subnormal but the rectal temperature is invariably raised to a moderate degree, 100 to 101 F It is possible that some severe cases of heat exhaustion will, if untreated go on to heat hyperpyrexia but as a rule the clinical picture remains true to type and the treatment is different. The prognosis, provided adequate treatment is given is excellent.

3. *Heat hyperpyrexia*

The essential factor is the failure of the heat regulating centres with the suppression of sweating, once the temperature reaches 108° F coma and convulsions ensue and the mortality rate is very high. The urinary chlorides are reduced.

Heat Exhaustion

The following description is based on a personal experience of thirty severe cases of heat exhaustion encountered in Iraq in British personnel over a period of years. A general impression was formed that there was a certain type of individual who was particularly prone to develop heat exhaustion—the lean, anxious, spare type with a low systolic blood pressure he was usually a sedentary worker and in 33 per cent of cases was a strict teetotaller over 63 per cent of the cases had not completed their first hot season. An analysis of predominant symptoms recorded the following results —

	Per cent		Per cent.
Dizziness	53	Suppression of urine	16
Vomiting	70	Anidrosis	10
Muscular cramps	26	Nausea	80
Constipation	43		

There were no fatalities amongst this series of cases so the prognosis, provided the condition is recognized and adequately treated, is excellent. In two cases it was necessary to recommend a transfer to a cooler climate. One of these cases was particularly interesting as although this patient had lived for over 10 years in the tropics this was his third attack and each attack had been sufficiently severe to necessitate the use of prolonged intravenous salines, and on two occasions his life had been in jeopardy His blood pressure was abnormally low for a man of 32 Systolic 103 diastolic 65 and I have noticed the same low blood pressure in several other cases.

Symptomatology

In some cases the actual onset is sudden but there is usually a premonitory stage during which the patient suffers from anorexia, weakness of the legs, headache and constipation for 2 or 3 days before collapsing In many instances this collapse occurs at night and bears no relation to exertion. The patient at this

stage shows all the symptoms of shock, a low blood pressure cold, clammy and profuse perspiration and mental apprehension and irritability nausea and vomiting may ensue, the vomitus eventually becoming bile stained. In the severe cases violent cramps in the abdominal and leg muscles are a marked

CHART 1

BAGHDAD AREA – HEAT EXHAUSTION
CLINICAL FACTORS

Case	Temp on Admission R	Temp on Admission M	Blood pressure on admission		Dizziness	Nausea & Vomiting	Cramps	Constipation	Retention of urine	Duration of Fever	Albumen
				Dia							
1		98°	88	46	–	+++	++	–	–	24 hrs	–
2		101°	–	–	–	–	+	+		2 days	–
3		98°	132	98		+	–			Nil	–
4		101°	90	60	–	+++			++	3 days	
5		100°	–		+	+	–			2	–
6		98°	118	72		++	++	+	+	2	–
7		98°			+					Nil	
8		101°	–							24 hrs	
9		98°						++		N I	
10		97°			–	+		+			
11		98°				+				24 hrs	
12	99°	–						++		2 days	
13		98°			+	+		+		Nil	
14	Subnormal		134	90	–	++		–		3 days	
15		99°			+	+				12 hrs	
16		99°	118	74	+					24	
17		99°	–			–		++		48	
18		101°			–			+		24	
19		101°				+		–	–	2 days	+
20		99			+	+				Nil	
21		99°	128	80	+	+	+			7 days	
22		100°	–		+	–				24 hrs	
23		98°	101	–	+	+++	++	+	++	Nil	
24	101°	–	100	78	+	++				4 days	
25	–				+	+		++		Nil	
26		104°			+	++			–	48 hrs	
27		101			+	+++	+	+	+	7 days (Treatment Experimental)	+
28		99°	98	60	+	++	+	+	+	3 days	
29		100°	85	50	+	+	+	+		2	
30		99°	105	65	+	+	–	–		2	

feature of the illness and the urine is invariably diminished in quantity The urinary chlorides are greatly diminished in all severe cases this is a most valuable aid to diagnosis. In the most severe cases there is retention and partial suppression of urine only 1½ to 2 ounces of urine being drawn off by catheter

in the 24 hours. An increase in the quantity of urine passed, together with an increase in the percentage of chlorides is an early and favourable sign of recovery. The axillary and mouth temperatures are often normal but the rectal temperature is invariably raised, usually to about 100° F. Rectal temperatures should be charted 2 hourly as in one case the temperature rose suddenly to 105° F. This was accompanied by maniacal delirium which rapidly subsided when the temperature had been reduced to 102°. Surg. Lieut. MACLEAN R.N.V.R. (1943), has reported an interesting case of heat exhaustion complicated by tetany due to hyper ventilation resulting from rapid respiration, and it is easy to see how this complicating factor can arise especially in unacclimatized nervous individuals. I personally have not encountered it. If the patient responds to treatment and the vomiting and cramps disappear a slight pyrexia appears which lasts for 2 or 3 days. In some cases headache persists for a week or 10 days after all other symptoms have disappeared.

TREATMENT OF HEAT EXHAUSTION

These cases should be nursed in the coolest ward in the hospital where an air-conditioned ward was available it was found that a temperature of 75° F. was the ideal temperature to maintain in the ward. Those cases with low blood pressures and symptoms of shock should be treated in the usual way by raising the foot of the bed; care should, however, be taken in the application of hot water bottles, and once the primary condition of shock has been relieved no further heat is to be applied for fear of creating a vicious circle. Hot coffee with plenty of sugar has been strongly recommended by R.A.F. medical officers at this stage, but I personally have had no experience of it. An enema of normal saline should be given if necessary but purgatives are to be avoided as they increase the dehydration. Copious fluids containing glucose and sodium chloride (20 grams to the l) should be given by the mouth, but if these are not retained or if the clinical condition warrants it intravenous NaCl 0·9 per cent. should be given by a saline drip; the intake and output of fluids should be carefully charted and, as previously mentioned, an increase in the urinary output and an increase in the urinary chlorides are the earliest and most reliable signs of recovery. In certain cases an alkalosis develops from excessive vomiting and as Professor NOAH MORRIS (1943) has pointed out the vomiting leads to loss of fluid which contains sodium with a great excess of chlorine. Accordingly carbonic acid is retained in the body fluids to satisfy the demands of base and an alkalosis is produced, the kidneys promptly respond by excreting an alkaline urine with excess of sodium bicarbonate. If the alkalotic condition persists long enough the continuous excretion of sodium causes too great a reduction in the osmolar concentration of plasma and tissue fluids. The osmotic pressure is more important than the pH and the kidneys conserve the sodium even although by so doing the alkalosis increases in intensity. Accordingly the urine now contains a relative excess of organic acids with the result that its reaction

is acid while a state of intense alkalosis exists in the body If now sodium chloride is supplied in sufficient amount the kidneys can immediately return to their task of diminishing the alkalosis without running any risk of imperiling the osmotic pressure of the tissue-fluids and the urine becomes alkaline. In 1930 I treated with success several cases of heat exhaustion with 2½ per cent. bicarbonate of sodium in normal saline, together with glucose by mouth or intravenously (MORTON 1932) In 1939–1942 I attained even greater success with the use of sodium chloride, 0·9 per cent. alone, together with glucose, and I am now firmly convinced that the good results obtained in 1930 were due to the sodium chloride and that the sodium bicarbonate is unnecessary and contra indicated If acidosis is present due to impaired renal function the best solution to use, according to Professor NOEL BAKER, is m/6 sodium lactate (1·8 per cent.) The lactate is rapidly oxidized to carbonate, thus enabling the sodium to combine with the excess acid substances and carry them off to be excreted in the urine.

To sum up 0·9 per cent. sodium chloride is the sheet anchor in the treatment of heat exhaustion together with glucose by the mouth or intravenously in order to provoke a diuresis and to treat the starvation the majority of these cases are suffering from and which, if untreated, may go on to acidosis.

DIFFERENTIAL DIAGNOSIS OF HEAT EXHAUSTION

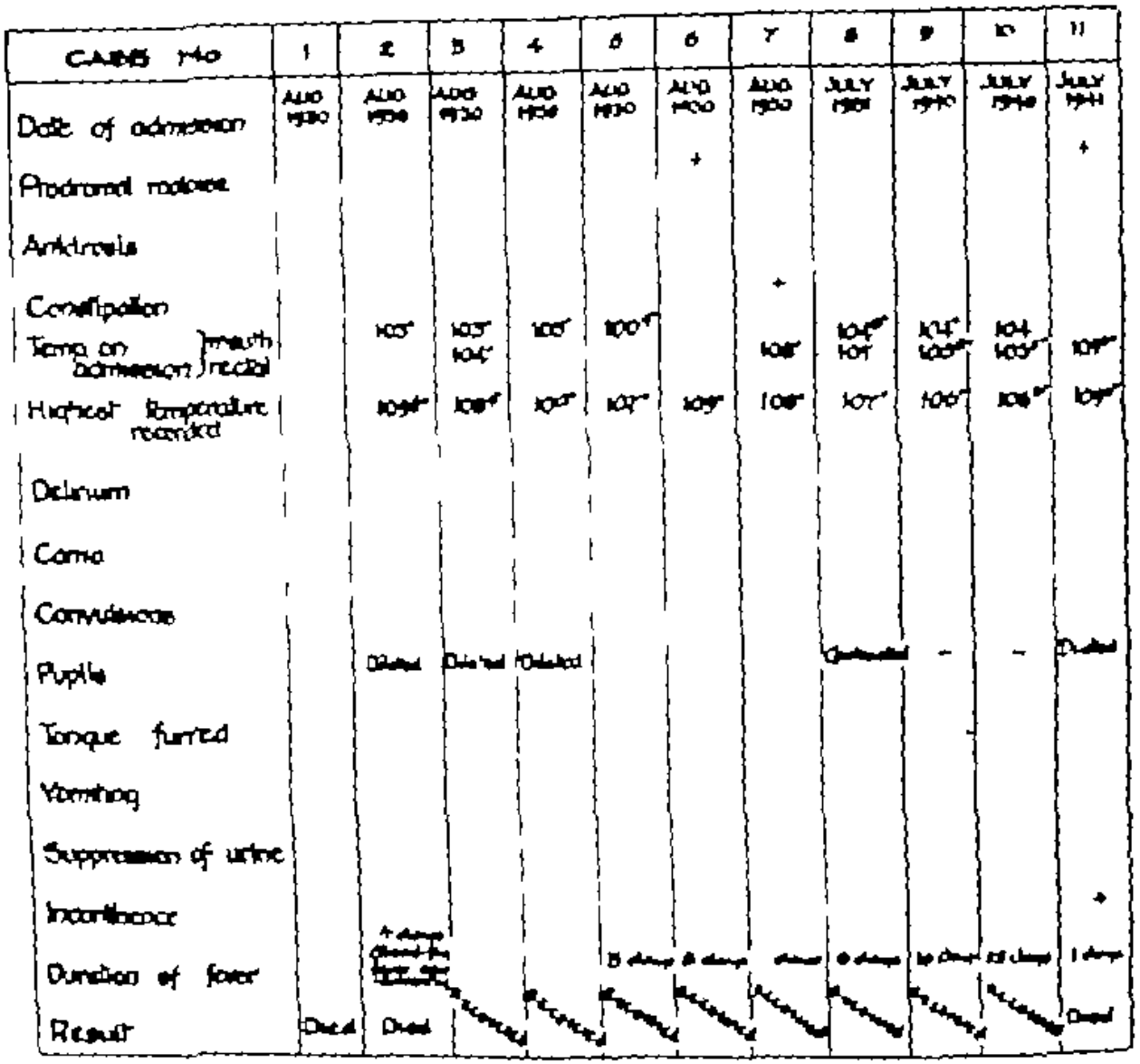
Malignant tertian malaria and food poisoning may cause confusion but parasites are usually easily found in the algid syndrome of malignant tertian malaria and in food poisoning diarrhoea is constantly present. An estimation of the urinary chlorides will clear up the diagnosis in doubtful cases of heat exhaustion as they are always markedly diminished. Fantus test for a rapid estimation of urinary chlorides is worth carrying out as a routine on all cases admitted to a medical ward during a heat wave. In one case of this series although the vomiting ceased as a result of treatment, the temperature continued to rise and *Bacillus typhosus* was isolated from the blood on the fifth day There is really an even greater risk of missing a surgical condition during an epidemic of heat exhaustion a case of intestinal obstruction was admitted to a medical ward fortunately the projectile vomiting led to its early recognition.

HEAT HYPERPYREXIA.

The following description is based on a personal experience of eleven severe cases of heat hyperpyrexia encountered in British personnel over a period of years A general impression was formed that there was a certain type of individual who was particularly prone to develop heat hyperpyrexia, the obese thick necked chronic alcoholic, with a high systolic blood pressure the average age of the patient was higher than in the heat exhaustion series and the mortality was 27 per cent. In the case of those individuals who did not conform to this description there were as a rule complicating factors such as

CHART *

HEAT HYPERPYREXIA — CLINICAL ASPECTS



malaria, urinary infection, oral sepsis and extreme physical exhaustion etc. There was only one teetotaller in this series and four of the patients were chronic alcoholics. An analysis of predominant symptoms revealed the following results —

Prodromal malaise 100 per cent. frequency of micturition, one case only
Anidrosis, 100 per cent.
Constipation, 18 per cent.
Delirium, 46 per cent.
Coma, 63 per cent.
Vomiting 54 per cent
Reflexes Knee jerks lost in 30 per cent., diminished in 70 per cent.
Convulsions, 46 per cent.
Hyperpyrexia 100 per cent. (criterion a temperature above 104 5° F.).

Stertorous breathing present in all comatose cases.

Urinary chlorides were invariably diminished in all cases where it was possible to obtain a specimen for quantitative examination. This has also been recorded by Dr FRANK MARSH of the A.I O C at Abadan. The general appearance of these patients was as a rule characteristic, the face was flushed, in some instances cyanosed, a dry burning skin was a constant feature and the blood pressure was usually raised. The onset was acute, in some cases the patient being admitted delirious -stuporous or in coma, and it was found that the more acute the onset the better the patient responded to thermantidote measures and the less tendency there was to relapse. If the temperature reached 108° F delirium and coma inevitably followed and it is doubtful if the temperature has remained at 108° F or over for more than 2 hours if recovery is possible although short periods at much higher temperatures such as 110 to 112° F have been followed by recovery (*Notes on Effects of Heat* 1943) I once saw a dying case of typhoid in the fourth week of the disease in Iraq whose temperature rose again and again to 112° F and it was pathetic to watch the frenzied strivings of the man's sweat glands to deal with the situation his eye sockets filled time and again with sweat which literally poured off his body in streams. Such an appearance is never seen in heat hyperpyrexia the hot dry roughened skin the bounding pulse, the flushed cyanosed face with congested conjunctivae of the typical acute case once seen is stamped indelibly in the memory My limited experience fully confirms Colonel HEARNE'S (1932) observation as to the value of the dry burning skin as an early sign of oncoming heat hyperpyrexia, and nursing orderlies should be trained to look out for it whilst recording pulse and temperatures a mere palpation of the thorax or axilla is sufficient. In the majority of the cases the temperature had settled to normal by the end of the week but in three cases a prolonged pyrexia associated with a furred tongue and a polymorphonuclear leucocytosis persisted for from 10 to 14 days. All laboratory investigations including blood cultures, agglutinations etc., were completely negative and the temperature only settled down after prolonged residence in an air-conditioned ward Two cases were transported by air from Basrah to an air-conditioned ward in an R.A.F hospital and it was amazing how these symptoms disappeared and their temperature fell to normal within 4 or 5 days whereas all previous thermantidote measures at Basrah had had no lasting effect. This enteric-like syndrome is very confusing if not recognized and a perusal of old hospital records showed that similar cases had occurred in previous heat waves and that a relative and absolute polymorphonuclear leucocytosis for which no cause could be found was a constant finding in this type of case.

TREATMENT OF HEAT HYPERPYREXIA.

The temperature must be brought down as quickly as possible to 103° or 102 5° F by sponging with iced water and the use of fans. It is essential to eliminate malignant tertian malaria and in any doubtful case intravenous quinine is indicated. In one of the fatal cases in this series although no malarial

parasites could be found, intravenous quinine had been given and postmortem malarial pigment was present in sections from the liver and spleen although no malarial parasites were found in smears from the brain and spleen. A temperature of 60° F was maintained in the air-conditioned heatstroke centre but as soon as the thermantidote measures had taken effect the case was transferred to the treatment ward which was maintained at 75° F as lower temperatures led to undue chilling of the patient and even at this temperature a blanket was appreciated. The patient was encouraged to drink large quantities of fluid containing NaCl and glucose but intravenous saline were not required in the hyperpyrexial type of case unless vomiting was troublesome, and in my experience they are rarely required as these cases are not usually dehydrated. Before resorting to intravenous saline it is essential to be guided by the systolic blood pressure haemoconcentration, etc. otherwise one may do more harm than good by overloading a failing circulation The nursing was considerably eased by the provision of the air-conditioned wards and in no case was a second cold sponging necessary a welcome contrast to our experience in the 1930 epidemic, when for 10 days in one patient the rectal temperature rose to 105° F from one to three times in the 24 hours necessitating repeated ice sponging and throwing a very heavy burden on the nursing staff The question of iced enemas is a very vexed point they are of value under active service conditions where water and ice are scarce, such as staging posts and on desert convoys, and here an iced enema of 0·9 per cent. normal saline is definitely indicated but by using them one deprives oneself of the recording gauge of the thermometer in the rectum and therefore we did not use them in our hospitals. Theoretically they are liable to increase shock. Convulsions and venous congestion were treated by venesection, about 15 ounces of blood being withdrawn with benefit and oxygen was administered when necessary In one fatal case lumbar puncture controlled the convulsions and the fluid was found to be under pressure but otherwise normal, the patient eventually succumbing to circulatory failure. The use of a magnesium sulphate enema to relieve headache in convalescence was found to be of considerable benefit, particularly in those patients whose cerebration was slowed and in whom there was no evidence of dehydration. Lumbar puncture, except as a means of diagnosis in doubtful cases is not recommended as a routine measure. The transition from the air-conditioned ward to an ordinary ward should be a gradual one. Neglect of this elementary precaution in one case of heat exhaustion led to a relapse necessitating further intravenous saline therapy We found that it was better to let the patients sleep in an ordinary ward at night once convalescence was well established, and the hours spent in the air-conditioned ward were gradually whittled down to zero prior to discharge from hospital.

Prophylaxis.

1 *Acclimatization.* The principle of confining trooping to the cool season so that newcomers gradually become acclimatized to the heat is an

excellent one any departure from this rule is fraught with danger but under war conditions is often unavoidable. It is essential that medical officers on troopships proceeding to the tropics should be familiar with the prevention and treatment of heat effects Incoming drafts should be disembarked in the early hours of the morning or in the evenings and the removal of heavy baggage, etc. should be carried out by acclimatized working parties and not left to the newcomer rendered soft and flabby after weeks of confinement on board a crowded transport.

2. *Air Conditioning* In certain hot localities in the Persian Gulf this is available for only 25 per cent. of the personnel but it is possible to so stagger the working hours that all the men can spend some hours off duty in an air-conditioned room This will, on the analogy of the furnace worker in temperate climates, do much to prevent the cumulative effects of heat and enable the body to repair the results of disordered metabolism.

3 *Propaganda During the Hot Weather* The slogan Drink more water Eat more salt was posted in all dining halls at the beginning of the hot weather In addition to this, during a heat wave in July 1940 when for over 5 days the temperature was over 120° F medical officers made a point of seeing that extra salt was added to the dietary and that men were warned to avoid getting constipated Working hours were adjusted so that men started work an hour earlier and stopped work at 11.30 a.m., and frequent inspections were made of welding shops tinsmith shops etc. Persian coolers were installed in these workshops containing an ample supply of cool water, to which salt was added, and the men were encouraged to drink little and often. As a result of these measures only two cases of heat exhaustion occurred a great improvement on our 1930 experience during an identically similar heat wave The year 1941, in which active operations occurred in Iraq Syria and Persia was fortunately one of the coolest summers on record, and it was owing to this meteorological blessing that we were spared a repetition of the Mespot of the last war when at the first battle of Ramadi over 300 cases of heatstroke occurred in one afternoon. In the hot summer of 1942 a severe outbreak occurred after I had left Iraq and I am hoping that some of our R.A.M C colleagues here may give us the benefit of their experiences.

Summary

1 The division of heat effects into heat syncope, heat exhaustion and heat hyperpyrexia is advisable as although borderline cases do occur the clinical picture is as a rule clear-cut and the prognosis and treatment are radically different.

2. *Heat Exhaustion* Electrolytic imbalance and dehydration appear to be of primary importance in the genesis of heat exhaustion The lean, spare type with a low systolic pressure is particularly prone to heat exhaustion and the age group is lower than in the heat hyperpyrexia cases. The quantitative

estimation of the urinary chlorides is a simple and reliable test in the differential diagnosis of these cases and in sodium chloride and glucose we possess a safe and effective remedy

If intravenous therapy is indicated this must be controlled by charting the intake and output and estimating the haemoconcentration, otherwise there is a risk of pulmonary oedema. The prognosis in heat exhaustion is excellent provided the condition is recognized in time and adequately treated, otherwise cases may die of circulatory failure or go on to heat hyperpyrexia.

3 *Heat Hyperpyrexia.* This is always a grave syndrome the mortality is usually at least 30 per cent. and may be considerably more. Alcohol and age are accessory and adverse factors and the condition is more frequent in the fat and plethoric The essential factor is the failure of the heat regulating centre with the suppression of sweating although in the more protracted cases it is probable that an auto-intoxication is responsible for the prolonged pyrexia. Thermantidote measures and the nursing of these cases in artificially cooled wards are the basis of treatment

4. *Prophylaxis* (*a*) Ample cool drinking water containing 10 grains of sodium chloride to the pint, together with a total consumption of at least 1 ounce of sodium chloride a day is a paramount necessity in all endemic areas during the hot weather (*b*) The provision of air conditioned or artificially cooled wards in hospitals in endemic areas is as essential as the provision of a well-equipped operating theatre

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DISCUSSION

Colonel A Sachs Air Commodore MORTON's paper is of particular interest to me as I arrived in Iraq just about the time he was leaving It therefore forms a valuable basis for comparison with the observations made during the hot weathers of 1942 and 1943 and I hope that mine will be complementary to his own. As Assistant Director of Pathology I had the opportunity of

touring Persia and Iraq and visiting hospitals where cases were treated under different conditions.

It was found that seasoned troops in good physical condition attained a high degree of resistance. Indians were not immune, but although the incidence among them was lower than in Europeans the case mortality was higher Gurkhas need the same degree of acclimatization as Europeans

Among important *predisposing factors* not usually stressed were lack of sleep and rest, insufficient food prior to a move, and poor physical condition caused by fatigue or by some previous illness *e g* malaria, sandfly fever dysentery diarrhoea and sea sickness. Illnesses associated with high fever or persistent vomiting were particularly dangerous It was found in workshops in the desert that by making réveillé later and so allowing an extra hour s sleep the men kept fitter and moreover there was no fall in output although the daily period of work was reduced by 1 hour

A group of cases which does not appear to fall into any of the types described is *sub-acute effects of heat* In the apyrexial or nearly apyrexial stage these cases were at first not recognized and were only diagnosed when they developed hyperpyrexia. They did not respond to treatment as well as acute heatstroke in a previously healthy individual Diagnosis was difficult in the pre hyperpyrexial stage as the symptoms were similar to other illnesses

The common early symptoms were headache feeling of exhaustion or off colour giddiness constipation or diarrhoea and anorexia. Not infrequently there was a change in the patient s normal behaviour *e g*., dullness, irritability restlessness or even insubordination. This stage may last from 3 days to 3 weeks but it was usually 2 to 10 days before hyperpyrexia developed

In the mild early cases rest in a cool atmosphere, with plenty of salt solution to drink, is all that is necessary In the more severe cases a cool atmosphere is essential, but these cases also require treatment for the marked dehydration and salt deficiency

If in the early stage treatment is inadequate, symptoms, although they may have passed off are liable to recur on exertion or re-exposure to heat.

A deterioration in the patient s mental condition, which may be maniacal, not infrequently develops with the hyperpyrexia. Coma and convulsions sometimes appear The problems of treatment are those of hyperpyrexia, but a large proportion of these cases died in from 1 to 4 days after the onset from circulatory failure and bronchopneumonia.

PATHOLOGY

After perusing postmortem reports and examining sections from fatal cases which occurred during the hot weathers of 1942 and 1943 it was possible to record certain constant observations.

The first group consisted of cases of hyperpyrexia who had died prior to the institution of intravenous treatment.

Macroscopically

The temperature of the body is high and in some cases apparently rises. In one case a rectal temperature of 115° F was recorded 3 hours after death.

Postmortem rigidity occurs unusually rapidly often within 1 hour and passes off much sooner than normal *i.e.*, within 6 hours.

On opening the body the peripheral vessels are found to be engorged with dark and fluid blood such as is seen in peripheral circulatory failure.

The cerebral vessels are similarly engorged and form a red network over the brain. The pia mater shows signs of oedema.

Petechial haemorrhages in the brain and small subpleural, subpericardial, subendocardial and subperitoneal haemorrhages have been observed in the majority of cases.

The mucous membranes of the stomach and upper part of the small intestines are so intensely congested that acute gastro-enteritis or even an irritant poison may be suspected.

The condition of the heart is generally characteristic. This is stony hard to the feel. It is believed that this is due to intense postmortem spasm of the myocardium.

The lungs are very haemorrhagic and congested and exude a blood-stained froth, which is also found in the air passages.

Microscopically

General Findings Degenerative changes of the parenchyma cells of the heart, liver kidneys and suprarenal occur early and have been found in post mortems carried out within 2 hours after death. After 24 hours the cellular element of the tissue has completely disappeared. This, to the inexperienced, would suggest acute antemortem necrotic changes in the liver kidney and pancreas. In view of the rapid early postmortem degeneration, it is impossible to decide whether antemortem damage has in fact occurred. The degeneration and cooked appearance of the organs is very characteristic.

Generalized engorgement of the vessels is a constant feature.

The presence of coarse granular pigmentation throughout the organs is suggestive of increased destruction of the red blood corpuscles. The cause of this is debatable.

Brain The vessel walls are swollen and have a hyaline appearance. It is probable that this change is partly degenerative, and partly physical as a result of an alteration in the osmotic pressure of the plasma. (A relative increased plasma protein content follows dehydration.)

Oedema is marked. This is both perivascular and perineuronal.

The Virchow Robin spaces are often filled with a pale acidophilic staining fluid. Sometimes R.B.C.s appear to have migrated through the walls. This is suggestive of increased permeability of the vessel walls to fluid and cells.

Varying numbers of small haemorrhages occur. In these areas the surrounding tissue is sclerosed. Thrombosed capillaries are frequently seen.

Chromatolysis occurs but again it is impossible to determine whether this is a postmortem or antemortem change.

Lungs.—The alveolar walls show the presence of haemorrhagic oedema. These changes appear to be sufficient to reduce the capacity of the air sacs which results in a diminished vital capacity of the lung. The findings are very similar to those observed in early cases of phosgene gas poisoning and are very characteristic.

The second group were treated cases of heat hyperpyrexia.

In the main, findings are similar to the untreated cases but depend to some extent on the quantity and rate of fluid given intravenously as cases of heatstroke are found to be particularly liable to develop pulmonary oedema.

When infusions have been given too lavishly there is an increase of fluid in the serous cavities and some oedema occurs in the kidneys liver and gut. The lung tissue is more severely damaged than in the untreated case. Marked pulmonary oedema is always present, and signs of bronchopneumonia are frequently seen.

In the brain there is an increased cellular content, probably due to proliferation of the neuroglial and microglial cells.

The third group were cases of effects of heat without hyperpyrexia.

This group consists of individuals who have been unable to acclimatize themselves. Hyperpyrexia is not a feature. Very often there is some underlying physical defect, or the condition may be a sequel to a previous illness due to effects of heat.

In these cases findings are modified. Fatty changes in the liver and heart, or signs of previous renal damage are superimposed.

Commentary

Some of the postmortem changes are undoubtedly due to physiological processes which are a sequel to the water and electrolyte loss. An impairment of the circulation follows the haemoconcentration, raised viscosity of the blood and the altered osmotic pressure of the plasma proteins. Eventually there is peripheral circulatory failure, of which signs are found both during life and postmortem.

It would appear that in the stage when haemorrhagic oedema of the lung has occurred the vital capacity is diminished, and some interference with the O_2 and CO_2 exchange must take place resulting in a condition of anoxaemia. This view is supported by the beneficial results obtained after oxygen administration in severe cases.

It is thought that there may be an important relationship between the anoxaemia and the morbid histological changes described.

As Air Commodore MORTON has remarked our knowledge of the biochemistry of the condition is in a state of flux, and until this is understood it is unlikely that there will be any great advances in treatment.

Lt.-Col. Robert Drew I have been most interested in Air Commodore Morton's valuable paper and I fully agree with him as to the predisposing causes. Most of the cases of heat hyperpyrexia seen by me were suffering from some intercurrent disease like malaria. Some of them were in hospital under observation or treatment in the dysentery wards and one patient who was being treated with atropine for a duodenal ulcer developed heatstroke. I remember seeing a patient with tetany similar to that described by Surg. Lieut. Maclean. The highest rectal temperature in the cases I have seen was 113° F. and in spite of this the patient recovered, though he had considerable mental impairment afterwards.

With regard to acclimatization: do people lose less sodium chloride in their sweat after living in a hot climate? I am not convinced by the evidence so far produced that acclimatized people lose less salt in their sweat. We are familiar with the work done by the Germans in this war on acclimatization. They put many of their soldiers into hot houses for a month before sending them to North Africa so as to accustom them to the heat, and few diseases due to heat occurred in this group. Although, in the Army we provide salt tablets and give as much salt and water as possible to the troops during the hot weather, I consider that acclimatization is a most important factor.

Prof. P. A. Buxton: Those who have seen something of heatstroke and the effects of heat in the Persian Gulf will be glad to have heard Air Commodore Morton put the modern view of the subject so clearly and well. Perhaps the most remarkable thing about his paper is the omission of all reference to urinals, red shirts, spine-pads and topees. His total omission of those superstitions is a very encouraging thing because one sometimes feels how slow the advance of medical knowledge and its applications may be.

A minor point to remember is that after a grave operation the risk of heatstroke is increased by bandaging and dressing. Lives have been lost because those responsible for surgical cases have not been informed of this risk.

I would rather look forward than back in relation to this problem of the unfortunate effects of heat, and I wonder whether we British are going to make sufficient use of air conditioning? The Americans are already far ahead of us in the construction of barracks for the housing and comfort of troops in the tropics. Already in America on the eastern seaboard the use of air conditioning is commonplace in the hot months in hotels and offices. Conditions are trying there, but nothing approaching to what they are where our men are serving now and may live after the war. Very serious attention should be given to the liberal provision of air conditioning in barracks (not only in a few wards) in those areas, but I am rather afraid it will not be done.

Colonel S. P. James said that Professor Buxton's remarks led him to ask a question. He had listened last week to a broadcast on the modern war training

of British troops in India. He had heard with surprise that the medical authorities in India have drastically changed their ideas as to what can and cannot be done without injury to health under the fierce Indian sun. The broadcast said that the old fashioned picture of troops protected by sun-helmets and spine pads should be forgotten and that the topee was dead.

The question he wished to ask was whether in fact the medical authorities in India have modified their views so drastically and, if so whether the new views are also held in Iraq and other tropical countries?

What are the reasons for the new practice? The broadcaster seemed to think that pride and "fashion had something to do with the change. He said that the men live mostly stripped and that they are very proud of getting beautifully sun browned He said, the really fashionable wear is the hat, Gurkha felt,* which is worn at all possible times and in all possible ways. A favourite way of wearing it was with the crown pressed down in the middle rather like the Homburg hat or like the tiny felt hat in which Mr WINSTON CHURCHILL used to be pictured by the cartoonists of 30 years ago Colonel JAMES ventured to say that if fashion was a chief reason for the change in headgear and other kit the British troops under training in India did not seem to him to be quite up to date. To be really in the fashion they should study a recent photograph of Mr WINSTON CHURCHILL that was published on page 62 of the Ministry of Information's booklet, *The Eighth Army* The photograph was taken during the PRIME MINISTER'S visit to Alamein in August. He is wearing a Cawnpore topee with a wide brim dark sun-glare spectacles, a battle-dress tunic and gloves He is carrying in one hand a fly-whisk in the other a white umbrella. The photograph doesn't show whether his tunic is lined with red or whether it has a spine pad but the whole outfit, in every other respect, is precisely what was strongly advised by the medical authorities in Mesopotamia in the last war

Is it true that all these excellent precautions against the sun are only the bogies of old fogies which have now been abandoned?

And about acclimatization is it the present view that by continually exposing a man's bare head and his naked body to the fierce Indian sun he becomes immune to heatstroke? In this connection he would like to mention an example of heatstroke which occurred in Mesopotamia during the last war Many will remember the practice adopted in that war of sending civilian specialists from England to various fronts to advise on medical and surgical arrangements and to send home reports of what they saw With one of the several Commissions which visited Mesopotamia in 1916 there came a famous brain surgeon. He was by no means a young man, but he had all the

* Experiments on the comparative efficiency of various types of sun-helmets and hats were described by COMBY in 1926 (*J trop Med. [Hyg.]* **29** 2) and by GLOVER in 1942 (*J trop Med [Hyg.]* **36** 3) The single-felt hats, such as the Gurkha hat, were found to be the least efficient of all types tested.

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ized but they were producing sweat of the same concentration as the unac climatized. I think that shows to a certain extent that the story that people lose less sodium chloride in their sweat when acclimatized is rather misleading I have done a certain amount of work in hot rooms and I do not believe when the evidence is sifted you will find that acclimatization leads to loss of less sodium chloride in the sweat.

Wing Commander Lee Potter I should like to reassure Colonel JAMES that the old bogy is not entirely dead During this war I have seen army officers wearing red lined shirts. I don t know whether they bought them as a protection against heat but presumably the tailor sold them for that purpose.

Major-General A G Biggam I would like Dr LADELL to tell us what he understands by acclimatization ? What change takes place during the process we call acclimatization ?

Dr Ladell said he was not able to answer this question.

Dr B McArdle then put forward the view that certain changes take place during acclimatization one of which is the earlier onset of sweating The rectal temperature of an unacclimatized subject may rise a degree or more before he starts to sweat, whereas the same man when acclimatized will probably start sweating before his temperature had risen more than about 0 2° F The acclimatized man also sweats more. American workers have recently shown that the energy expenditure—and the bulk of this has to be dissipated as heat—of the unacclimatized man doing a given amount of work in the heat is con siderably greater than that of the acclimatized person. The effect of acclima tization on the cardiovascular system is striking and occurs mainly in the first 2 or 3 days. The body is able to provide a better blood supply to the skin resulting in a higher skin temperature, and therefore in greater evaporation and cooling than would otherwise be the case.

I have never been in the tropics but it strikes me that the umbrella is a very sensible thing The radiant heat of the sun is a potent source of heat, and shading is an obvious remedy

Dr Waterlow There are the clinical aspects of the paper One or two things Air Commodore MORTON has not mentioned and if we could get further information about those points it would be interesting We saw a number of cases that corresponded almost exactly to his description of heat exhaustion. Air Commodore MORTON says that the blood pressure in these cases was invariably low but I could not agree with that from what I saw and some of our cases were extremely severe. About three times out of thirty we got pressures of 80 or so but the most striking abnormality was the reduced pulse

pressure 20 instead of 40 to 50. These low pulse pressures were never seen in normal subjects. I formed the opinion that this lowering of the pulse pressure is of great diagnostic value. Otherwise it would be easy to say "This patient has a systolic pressure of 110 and is therefore all right." I noticed that some of the figures of Air Commodore Morton's chart were of the same kind. Another point is the kind of case characterized by an abnormal skin—a dry skin and reduction of sweating but not hyperpyrexia. The rise of temperature rapidly disappears on admission to hospital but the skin remains abnormal for a long time—2 or 3 weeks. In most of these cases there is little else wrong except complaints of weakness, dizziness, and so on. The only other striking abnormality is the secretion of a large amount of urine, up to about 9 litres, which is greatly abnormal. We should be very much interested to know if Air Commodore Morton found cases of this kind.

The President (Sir Harold Scott). I have very little to add before I ask Air Commodore Morton to reply. One thing has always puzzled me. In the West Indies, we habitually wore topees during the day but would go out without hats to play tennis in the heat of the sun, or at any time of the day and in the course of a good many years there I never saw a case of sunstroke or heatstroke. Sunglare was quite common. What is the explanation? As regards the reaction of the white man and the negro to physical exertion, it is a well-known fact that the black skinned man when he starts working sweats very easily and early and in small beads, and evaporation begins earlier than with the white man doing the same work. The latter does not sweat so easily and when he does it pours off in streams. I wonder if that has anything to do with acclimatization? I was very glad indeed to hear Air Commodore Morton's paper but what interested me equally as a pathologist, were Colonel Sachs's remarks on pathology and the details he gave I do not think are mentioned in the textbooks. I hope he will publish these findings. I think in the paper calculation in percentages on only eleven cases is apt to be misleading the difference between a 100 per cent. and 80 per cent. is very little. It reminds me of a paper on anthrax which I was reading recently where the writer said it was a 100 per cent. fatal in carpenters but a 100 per cent. recoveries in clergymen. I found in the author's list of cases that one carpenter got anthrax and died and one clergyman got it and survived.

Air Commodore Morton (in reply). I was glad to hear Colonel Sachs discuss the postmortems. I had three of these cases, and came to the conclusion that many of the findings we got were due to postmortem changes. The mortuary was 130° F. to 140° F. extraordinarily hot, and I realized very quickly that postmortem changes rapidly occurred. I sent a brain to a friend of mine, a morbid histologist, and he wrote back that he found very few changes in the brain that could not be put down to early postmortem changes but

I found widespread small petechial haemorrhages and the left ventricle was stony hard in all these cases On the whole the changes were similar to those of Colonel SACHS but obviously on three cases one was unable to draw any hard and fast conclusions I agree with our PRESIDENT as to the fallacy of percentages in such a small series of cases. As regards housing I agree with Professor BUXTON and I think it most important One can nowadays for £100 buy an air-conditioned cabinet, and most of the people in the Anglo-Iranian Oil Company have got these. There is no reason at all why every hospital in the Middle East—Persia, Iraq and the hot parts of India—should not have an air-conditioned theatre. I have seen two cases die of hyperpyrexia after operation one had been given atropine as a premedication, a dangerous thing in the hot weather the other had not. As far back as 1930 I stressed the fact that air-conditioning in theatres was very necessary Surgeons having to operate in hot weather are deterred very much by the risk of heat hyperpyrexia. I think in housing we should be as up to date as the Americans, and I have been most impressed with the way Americans have built their barracks out in the East, insisting on air-conditioning and refrigerators. The next thing is the question of topees, and I was very much interested in Colonel JAMES's remarks I believe the khaki felt hat is perfectly all right in countries like West Africa and Burma because there you are not dealing with extremely high temperatures but I would not like to spend a day in the sun in Iraq without a topee. During our scrapping out there we had some young army officers and I was sent out with some of them to try and provide a water supply at a village we had captured These boys had just come from the Western Desert and looked upon themselves as extremely tough. They wore ordinary pill box hats. I asked them, What about topees? They replied We did not use them in the Western Desert. I said This is not the Western Desert this is Iraq the shade temperature to-day is 117° F and I think you ought to borrow topees. But they would not. I took them down in a launch. It was an open launch and on the way back I saw two of the boys looking rather funny one said, I am not very well and shortly afterwards collapsed, and we spent the rest of our time pouring Euphrates water over him. If one has got an extremely good head of hair one can risk going about without a hat, but the cranium has a big blood supply and if the direct rays of the sun beat on the cranium it tends to overheat the blood generally and that is the reason for the topee. That is the advantage of the topee, but spine-pads I do not think necessary We have not used them for years, but topees I would recommend for Iraq Umbrellas I quite agree are far and away the most ideal thing but rarely practicable. Our sisters never wore topees but invariably carried umbrellas A word as to foot wear I am convinced that boots, especially heavy boots tend to push up the temperature of the body very considerably On the 24th July 1920 during the Arab rebellion, eighty men of the Manchester Regiment were taken prisoners by the Arabs, they were stripped and

marched barefooted for many miles during the heat of the day and yet not a single case of heat effects occurred amongst them, to everyone's amazement. I think the fact that they were almost naked and bare footed was a big factor in preventing heat hyperpyrexia. In the end their treatment was good and only one died in captivity. I have not seen the dry condition of the skin Dr WATERLOW has described, nor did I notice the reduced pulse pressure he records as estimations of diastolic pressure in collapsed cases are open to fallacy we might have missed it in some cases. The question of acclimatization is of course of paramount importance in the prevention of heat effects, as Colonel DREW has stressed. Purely out of curiosity I took my temperature after three hard sets of tennis in July with an afternoon shade temperature of 110° F. It was hard exercise with the sweat pouring off me in streams there was no rise of temperature at all either at the time or half an hour later. I was extremely surprised at this result and put it down purely to acclimatization.

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COMMUNICATIONS

LIZARD FILARIASIS AN EXPERIMENTAL STUDY

BY

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INTRODUCTION

Little is known of the stages of development of the human filarial worm *Wuchereria bancrofti* from the time of entry of the infective larvae through the skin to the fully grown forms which are met with in the deeper lymphatics in the mesentery the lymphatic glands or in the testis. During the course of an enquiry into human filariasis it was thought that a study of the life cycle of the lizard filaria might give a clue to the stages of development, since both the parasites and their embryos are similar while the insect vector the mosquito *Culex fatigans* is identical It has also been found that the developmental stages of the parasite in the mosquito the period of maturation of the larvae, the effects of environment such as temperature and humidity and the effects of hyperfilariation on the insect vector are all closely similar both for human

* This study was supported by a grant from the Indian Research Fund Association and was part of a Filariasis Enquiry undertaken at the Andhra Medical College Vizagapatam. Our grateful thanks are due to Dr C. G Pandit Director and Dr K. P Menon Assistant Director King Institute Guindy for supplying us with naturally infected lizards to start the investigation.

and lizard filariae. The lizard *Calotes versicolor* is the garden lizard of India that is sometimes called a blood sucker because of its variegated colour pattern. It is closely similar to the *Calotes mamas* and is also called a chameleon from its changing tint which is most marked in the male, especially during the breeding season. Filarial infection of the lizard was first noted by CASTELLANI and WILLEY (1905) and the parasites subsequently described by VON LINSTOW (1906) under the name *Filaria flavescens* first suggested by their discoverers. Later PANDIT PANDIT and IYER (1929) described a similar parasite which was called *Conspiculum gundiense*. However BAYLIS (1939) is inclined to regard both these as identical and has suggested the name "*Conspiculum flavescens*." PANDIT PANDIT and IYER (1929*a*) have also described the developmental stages of the parasite in the culex mosquito and showed that infection of lizards is possible experimentally by the bites of infected mosquitoes. Natural infection of lizards is found to vary very considerably in different localities. This is high in Madras while it has not so far been found in Vizagapatam in any of the seventy specimens examined.

MATERIAL AND METHODS.

Naturally infected lizards were obtained in batches from the King Institute, Guindy for starting the experimental work. Laboratory bred culex mosquitoes were then infected with the lizard filaria by feeding and after the full course of development in the mosquito the filarial larvae were collected when they had come up to the proboscis. These infective larvae were kept alive in normal saline and subsequently injected in numbers subcutaneously into healthy lizards obtained at Vizagapatam after their blood had been repeatedly examined for any natural infection. The artificially infected lizards were killed at specified intervals and the different developmental stages of the parasite obtained by dissection. From other infected lizards, tissues were obtained and fixed immediately in Bouin's fluid and Helly's fluid for histological study. For each stage of the parasite, the time after injection, the site of recovery and the morphology of the parasites were all recorded and photographs of the developing forms obtained. The parasites were examined fresh and subsequently fixed and mounted in lactophenol. For histological study the tissues of infected lizards were stained by Ehrlich's haematoxylin and eosin by Masson's trichrome stain, Maximow's azur II eosin and Leishman's stain.

RESULTS.

The Stages of Development.

1. *Infective larvae*.—These have been described by PANDIT PANDIT and IYER (1929). They measure 1,000 to 1,250μ in length by 19 to 20μ in width. The cuticle is smooth, the oesophagus is continuous with the intestinal canal which forms a well developed tube.

2. *Second day of development* —The cuticle is smooth, the tail and head ends are almost of the same shape, but the tail is more pointed and narrow The head measures 16·6μ and the tail 12·5μ in width The intestinal canal runs through the whole length the mouth is simple without any papillae and the differentiation of the oesophagus just commencing Anterior to the middle of the oesophagus is a constriction caused by the faint transverse striation of the rudiment of the nerve ring The anus is subterminal without any papillae. The protoplasm is highly granular especially in the middle of the body

3 *Fourth day of development* —This is a small cylindrical worm with the head 5·4μ wide and a narrow tail end 2·1μ wide. The mouth is simple and the oesophagus long with a narrow anterior part and a wider posterior part separated by the faint transverse striation of the nerve ring at its middle. There are two pyriform thickenings on either side of the commencement of the oesophagus extending for about a quarter of the length of the anterior oesophagus. The intestine is tubular and uniform in diameter At the anal opening a cloacal bulge can be made out with a cloacal papilla opening at the base of the tail which tapers from this point. Reproductive organs are not developed and the sexes not differentiated.

4 *Fifth day of development* —The worm is similar except that the posterior end of the oesophagus is constricted and beginning to be demarcated into a segment. The posterior third of the intestine is narrow and curved to one side to accommodate a thick granular mass probably the future reproductive system

5 *Twelfth day of development* —The general shape of the worm is similar The oesophagus is thicker muscular and longer the paraoesophageal thickenings well defined and the nerve ring distinct. There are two well defined uterine tubes in the female growing from a solid column of cells in the body wall, the vaginal bud. The larger caudal tube winds round the intestine to a narrow terminal portion. The cranial tube is much narrower and tapering Both are greenish yellow in colour The intestine shows a well defined cloacal constriction and a terminal bulbous part consisting of a large median and a small lateral lobe. There are two well defined papillae on either side of the cloacal opening

6 *Sixteenth day of development* —The sexes are now defined. The *female* worm is cylindrical thicker and longer than the male. The body gradually narrows after the anal opening into a thimble like blunt round tip The mouth is simple and a little below the general level. The oesophagus has a thick muscular posterior bulb with the nerve ring at the junction between the anterior fifth and the posterior four fifths. The vaginal orifice appears in the middle of the body as a thick muscular sphincter The muscular vagina extends caudally with a dorsal convexity for 1·5μ and curves back to a point from which the two uterine tubes proceed and twine round the intestine as the caudal and cranial branches. The *male* shows a spicule like structure at the cloacal opening while the tail shows a tendency to be ventrally coiled. The coiled testicular tubules are narrow and transparent.

7 *Twenty-first day of development.*—The *female* is by now much longer than the male. The cloacal papillae are well developed, but post-anal papillae are indistinct. The intestinal canal is brown in colour and shows at the commencement an isthmus tube which is not well defined in the male Coils of uterine tubes extend from the posterior oesophagus to the tail The vaginal opening is well defined at about the middle of the worm. The *male* shows a ventral coil of the tail of about one and a half turns. The oesophagus has a short stumpy anterior part and a wide cylindrical posterior portion of about five sixths of the length, with the nerve ring at the junction The narrow testicular tubules encroach into the body cavity round the posterior oesophagus. The alimentary canal is brown in colour and gradually tapers down to the anus where it opens along with the vas between the cloacal papillae. The testis is long and tubular and much coiled. From its posterior end there is a short thick connecting tube which joins the vas which widens as it passes alongside the intestine to open at the cloacal aperture. The two spicules appear as one mass which is short, blunt and brownish in colour One spicule is quite distinct while a trace of the other is embedded in the first, both lying inside the cloacal aperture. The cloacal papillae appear as one plateau on the ventral aspect of the tail with cuticular depressions on either side. The plateau is divided into a broader proximal and a smaller and narrower distal part with the cloacal opening a little behind the centre.

8. *Thirtieth day of development* —The *female* shows a faint transverse striation of the cuticle its tail is not tapering but rounded. It has prominent anal papillae from which there extends a transverse dorsal cuticular thickening

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DIAGRAM.

Camera lucida drawings of the developmental forms of the lizard filaria, *Cosmocercoides gerrardiensis*

FIG. 1 Infective larvae

FIG. 2. 4th day form note the central granular mass.

FIG. 3 5th day form oesophageal junction and granular mass more marked.

FIG 4 12th day form oesophageal demarcation and nerve ring definite

FIG 4a Tail end.

FIG. 4b Middle of body showing early sex differentiation genital opening and uterine tubes

FIG 5 16th day form, head end with nerve ring, oesophageal bulb

FIG 5a 16th day form, tail end.

FIG. 6 16th day form head end showing isthmus tube

FIG 6a. Tail end showing spicule-like structure.

FIG 7 21st day form male, head end showing oesophageal bulb

FIG 7a. Tail end showing subequal spicules cloacal aperture, wavy vas and intestine.

FIG 8 and FIG. 9 Female and male 30th day

FIG. 10 and FIG 11 Female and male, 45th day

FIG. 11a and FIG. 11b Head end and tail end of 45th day male

FIG. 10a Tail of female 45th day showing anal papillae.

Figs 1—7 × Ca. 66 Figs 8 9 10 11 × 11 Figs 10a, 11a, 11b × 36.

DIAGRAM.

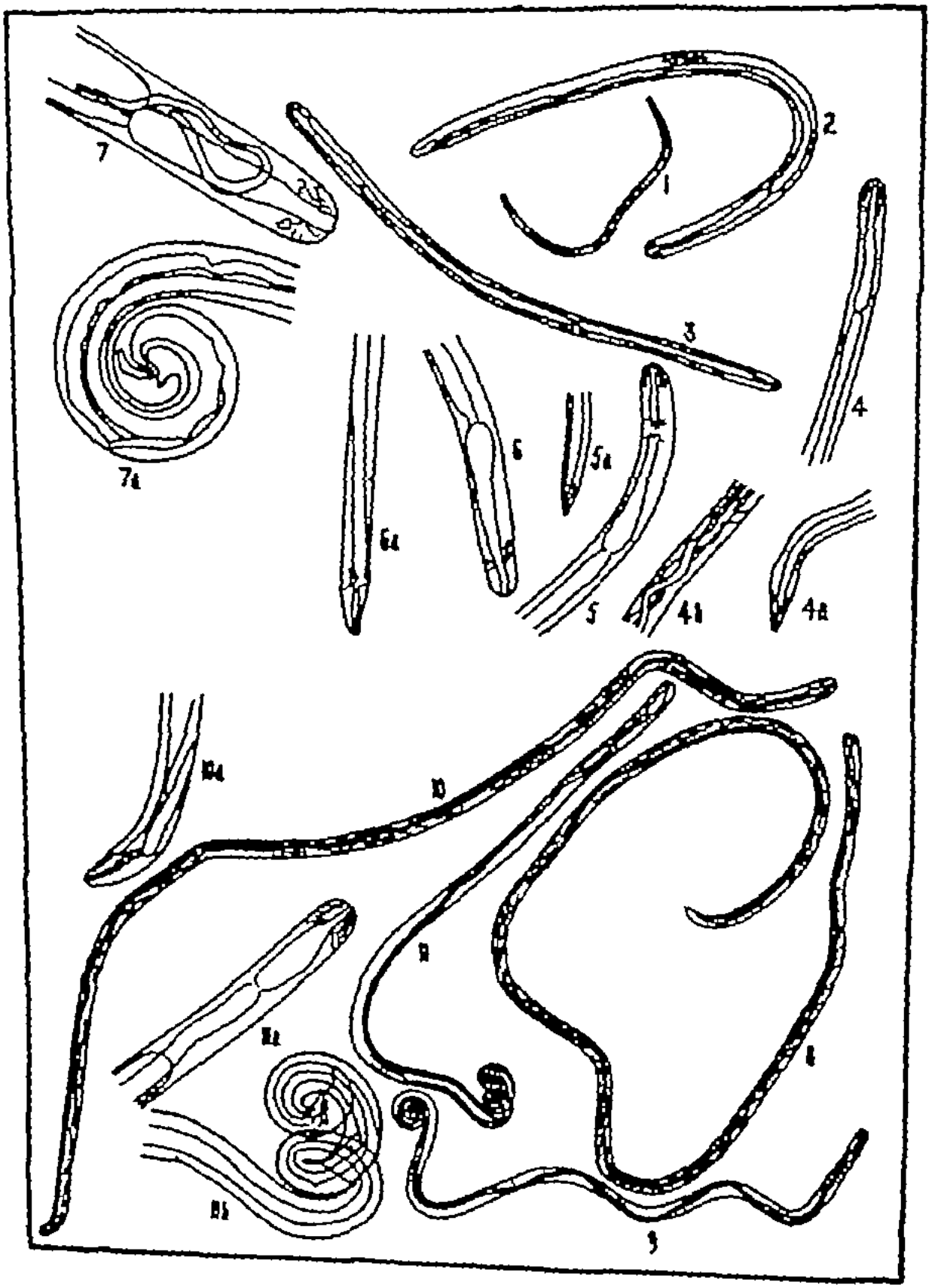

TABLE II

FEMALE REPRODUCTIVE ORGANS.

Day	Distance of Genital Tubercle	Anterior limit of Uterine Tubes from Head End.	Posterior Limit from Tail End	Dimensions of the Ovum.	Remarks.
12th	2·039 mm	1 133 mm.	1 1 mm.		Thickness of the vagina, 0 038 mm. Length of the vagina, 0·006 mm. Diameter of the genital orifice, including the sphincter, 20 μ. Length of the spina, 202 μ. Thickness of the vagina 0·033 mm.
18th	4 043 mm	1 106 mm.	8 175 mm.		
1 t	?	0 054 mm.	0·48 mm.		
30th	?	0 6 mm.	0 87 mm.	16 μ × 14 μ	
45th	17·9 mm	0 41 mm.	0 30 mm.	25 μ × 20 μ	Five pairs of post-anal papillæ. First pair, 41 μ × 41 μ. Third pair 33 μ × 80 μ. Last pair 22 μ × 33 μ.

TABLE III.

MALE REPRODUCTIVE ORGANS.

Day	Proximal Spicule				Distal Spicule				Distal limit of Test Tube from Tail End	Anterior limit from Head End.	Isthmus Tube.
	Length	Width. Base	Neck	Tip	Length	Width. Base	Neck	Tip.			
18th	The two spicules could not be made out separately Length, 80 μ Breadth, 30 μ								816 μ	683 μ	20 μ × 37 4 μ
21st	They could not be well made out separately Length of the spicule excluding cranial process, 121 μ									354 μ	29 μ × 80 μ
30th	137 5 μ	58 μ 58 μ	20 μ 17 μ	12 5 μ 8 μ	106 μ	70 μ	25 μ	12 μ		0·8 mm.	37 μ × 66 μ
45th	0 154 mm.	0·068 mm	0 016 mm	0·012 mm.	0·156 mm.	0·080 mm.	0·066 mm.	0 012 mm	1·95 mm.	2 0 mm.	40 μ × 80 μ

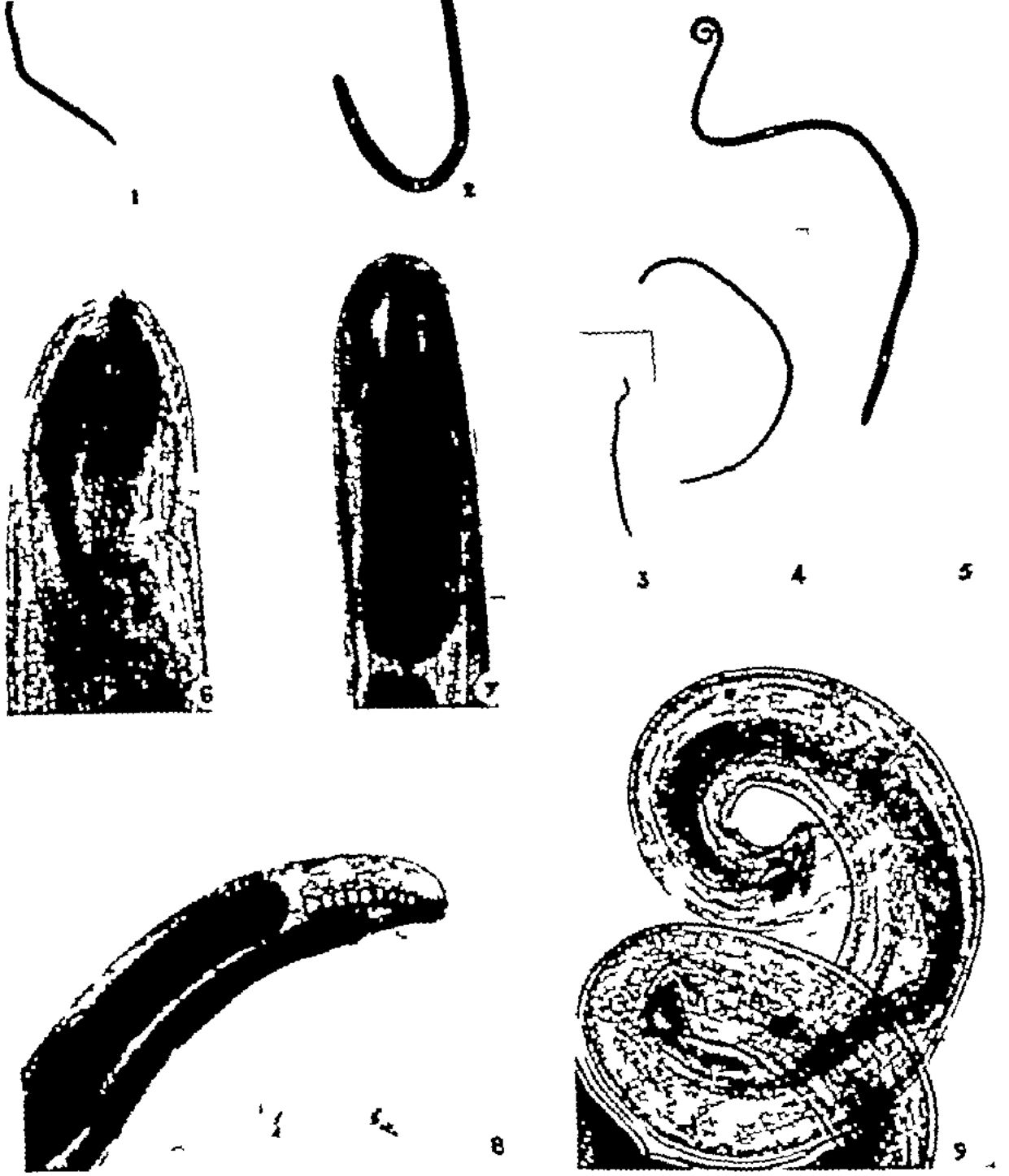

PLATE I

DEVELOPMENTAL FORMS OF THE FILARIA IN THE LIZARD (photographs)

FIG 1 The developing worm 24 hours after injection. × 27

FIG 2 The 4th day form. × 27

FIG 3 The 12th day form. × 7

FIG 4 The 16th day form. × 7

FIG 5 The male 21st day of development. ×

FIG 6 The head of the female showing the oesophageal bulb and the encroaching uterine tubes 45th day of development. × *ca* 62

FIG 7 The head of the male 45th day of development. × 62.

FIG 8 The tail of the female showing the five pairs of post-anal papillae appearing in a line × 62

FIG 9 The uncoiled tail of the male 45th day of development.

PLATE II

1 & 2 the oedema of the forelimb of an infected lizard.
The black arrow indicates the worms in the mesentery
3 the worms lying free in the mesenteric sac. × 6
4 the worms in the lymphatics of muscle of limb × 6

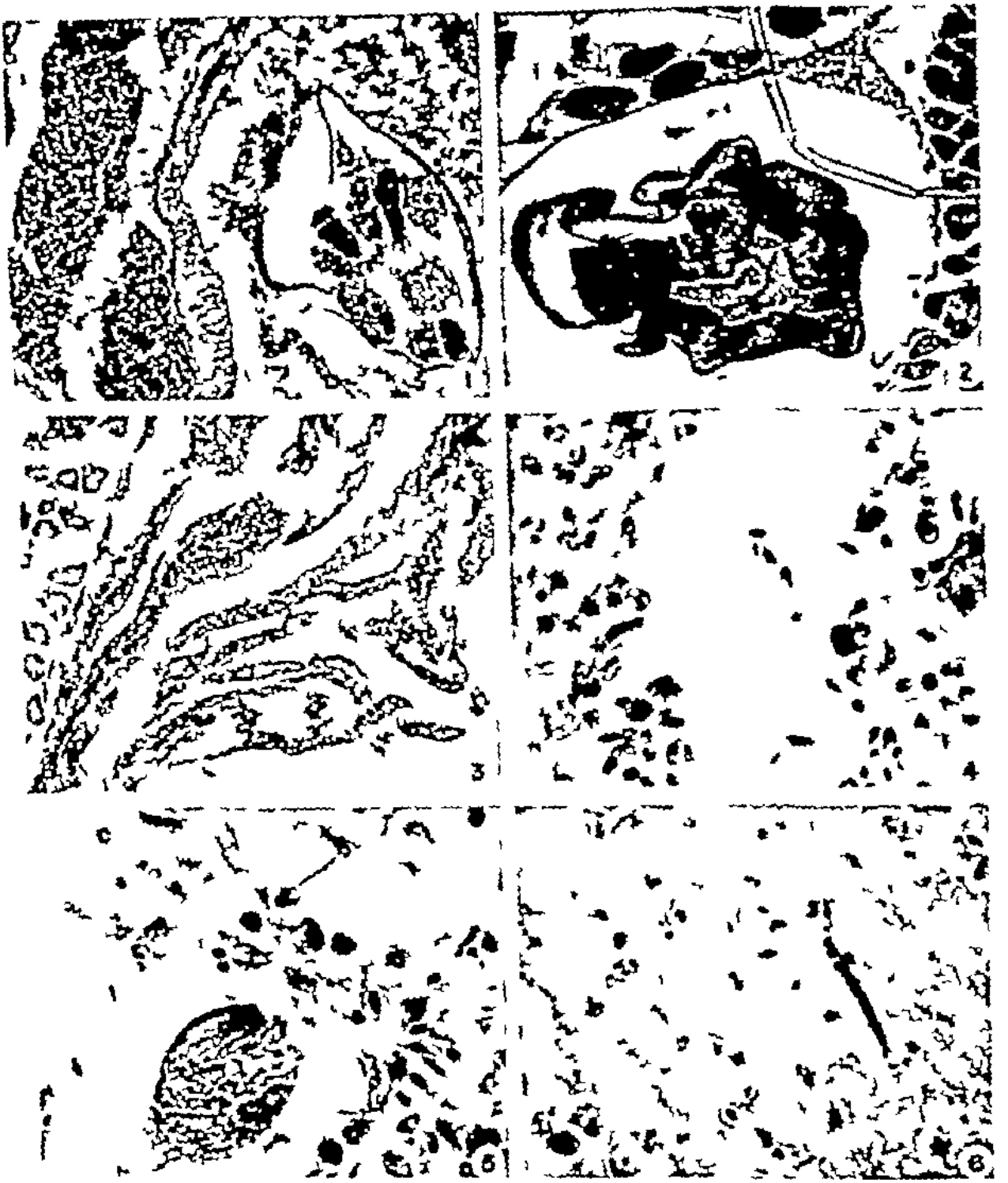

PLATE III

FIG 1 Female worm presumably alive in a lymphatic vessel near a vein in the limb The uterus is filled with ova and developing microfilariae There is little inflammatory reaction. × 80

FIG 2 Female worm in a lymphatic vessel in muscle Note the accumulation of macrophages at the periphery × 160

FIG 3 Lymphangiomatous area in the muscles of the limb near an adult worm. × 80

FIG 4 Lymphangitis showing macrophages alongside the wall of the affected vessel × 600

FIG. 5 Focal inflammatory changes around muscle bundles × 600

FIG. 6 Eosinophilic coagulum with disintegrating microfilaria and leucocytes in the sheath of muscle × 600

(Figs. 1—6 stained with haematoxylin and eosin.)

PLATE II

FIG. 1 shows the oedema of the forelimb of an infected lizard.
FIG. 2 The black arrow indicates the worms in the mesentery
FIG. 3 shows the worms lying free in the mesenteric sac. × 9
FIG. 4 shows the worms in the lymphatics of muscle of limb × 9

10 *The adult worms* —These have been fully described by PANDIT PANDIT and IYER (1929) The *female* is described as 95 mm. long and 0 73 mm. wide at its middle The male averages 28 mm. in length and 0 3 mm. in width at its middle. Histological studies of sections of the mature worms have shown the formation of the embryos inside the uterine tubes. At first these appear as faintly eosinophilic ovoid cellular masses without any definite egg shell and appearing like segmenting blastomeres Faint basophilic granules appear in these spherules they become larger the cluster of cells becomes irregularly ovoid in shape, then sausage-shaped and coiled and enclosed in a membrane These finally become elongated to form early embryos During this stage the basophilic granules become more prominent increased in size, and gradually arranged in the pattern met with in the microfilariae. Sections of the mature females show all the stages of development of the embryos inside the coiled uterine tubes which surround the central intestinal canal In the *male* the testicular tubules are on one side. They show long ovoid parallel columns of basophilic cells which become studded with very fine basophilic granules arranged in clusters like rosettes Later these granules become coarser and lanceolate and possibly represent the homologues of the spermatids

THE DEVELOPMENTAL CYCLE AND ITS SITE.

The infective larvae injected into the limbs subcutaneously migrate to the lymphatic vessels in between the muscle fibres where they increase in size. Later they migrate into the pelvic cellular tissues and from there to the mesentery The mesentery of the lizard is a thin walled lymphatic sac without adipose tissue and lined by two layers of endothelium, one from the peritoneal reflexion and the other forming the lining of the cavity Here they lie in between the layers of peritoneum inside the dilated lymphatic sac (Plate IV Fig 1) With regard to the forms of development the larvae from the mosquito show the demarcation of the oesophagus by about the 4th day while about the 12th day the genital tubercle and the uterine tubes appear in the female. The development of the male genital organs appears late as compared with the female where differentiation has been noticed on the 12th day In 21 days the sexes are well differentiated and the spicules developed in the male. The alimentary canal becomes covered over by the uterine or testicular tubules Gradually the features of adult worms appear the colour becomes browner with age, the uterine and testicular tubes increase in size and fill up the body cavity In the mature female microfilariae may be seen at the vaginal end. Microfilariae have not been met in heart or peripheral blood till the 41st day but have been found in most invariably in 72 days so that the average period of maturation appears to be about 58 days. It has further been noted that the larvae leave the site of injection for the first 2 days From the 4th to the 16th found in the lymphatics of the muscles of the limbs Migration to the mesentery is between the 16th and 21st day In the

mesentery or in the limbs development takes place actually inside dilated lymphatics. Infection of the mediastinal tissues may sometimes be met with by the migration of the worms, but small developmental forms are not found in the lung in any of this series. Forms recovered by dissection have shown that the activity of the worms is marked till about the 4th day they then gradually become sluggish and still later by about the 16th day activity is somewhat resumed. The site of maturation of the worms is mostly in the lymphatics of the mesentery or the retroperitoneal tissues, fairly frequently in the lymphatics of the limbs and occasionally in the peribronchial and mediastinal lymphatics. Rarely infection of the pericardium is followed by the entry of the worm into the auricular muscle.

THE EFFECTS ON THE LIZARD

The lizards show no discernible effects in the early stages of infection. If the infective dose is small, even in the later stages with adult worms in the mesentery and microfilariae in the blood, there are comparatively few noticeable changes in the lizard. Hyperfilariated lizards are dull, inactive, and do not exhibit the characteristic colour changes of the skin. They make no attempt to escape when the cages are opened, but remain stationary There is also a disinclination for food and no active attempts are made to catch the prey This torpor gradually increases till the animal dies. Visible oedema is not common. Only one case in this series showed increasing oedema of the fore limb which was the one infected. This started as swelling of the antebrachium which involved the cubital fossa and gradually extended to the brachium in about 4 days. The affected limb was always kept stationary The swelling was translucent and had extended to the distal part of the limb The oedema was in lobular masses with intermittent ring like constrictions. During this period the blood showed microfilariae only in scanty numbers. Bacteriological examination of the fluid was inconclusive.

THE PATHOLOGICAL LESIONS.

Histologically it could be demonstrated that the habitat of the parent worms is the lymphatic system. In the mesentery they lie inside lymphatic vessels. In the limbs the young forms migrate to the lymphatics of muscles and develop (Plate II Fig 4). Occasionally they lie in lymph spaces. Around the mature worms well defined changes appear in the lymphatic vessel. These undergo marked dilatation and hypertrophy with the development of plain muscle fibres in their walls as in human filariasis. Lymphatic obstruction shows itself in the formation of cavernous lymphangiomatoid areas in continuation with the affected vessel (Plate III, Fig 3). Polypoid projections from the wall extend into the lumen. At first these consist of vascular buds as in granulation tissue, but later they take on the characters of the vessel wall from fibrous tissue formation. While oedema is not visible to the naked eye, histologically the muscle

bundles are separated by oedematous fluid which is also seen in the sheaths of muscle as well as in the loose connective tissue around Slight but definite inflammatory changes consist in the accumulation of cells with lobed nuclei similar to the leucocytes, cells of a lymphoid type and particularly cells of the macrophage series The latter accumulate inside the lymphatic vessel and show phagocytic activity to dead and degenerate microfilariae and cell debris The cytoplasm of these cells is filled with vacuoles of variable size and the nuclei are round and vesicular with well defined nuclear membrane and central nucleoli Cells resembling plasma cells are also met with. There is little encapsulating reaction round the live worms which lie free inside the lumen while the cells appear at the periphery of the vessel. Around parasites which appear dead and disintegrating a series of changes is evident commencing with the accumulation of eosinophilic coagulating fluid which becomes infiltrated with cells of the leucocyte series, macrophages plasma cells and lymphoid cells. Eosinophilic leucocytes are not evident as in human filariasis. These eosinophilic coagula are bound together by coarse masses of fibrin which gradually becomes firmer and granular Different grades of the reaction are seen if a number of dead worms are examined. Where the body of the worm has greatly disintegrated the inflammatory coagula appear to undergo a process of organization, while proliferation of cells of an epithelioid type may occur as in tubercle formation (Plate IV Fig 4) Multinucleate giant cell formation has not so far been met with, but clusters of lymphoid nuclei at the periphery of these cell masses suggest symplastic fusion. These inflammatory coagula are found not only around the parent worms, but around disintegrating microfilariae as well as on the walls of the affected lymphatic vessel. The polypoid lymphangitis and lymphangiectasis would thus appear to be the result of the organization of such coagula. These reactions are on the whole much more marked around dead and disintegrating parasites than around healthy worms Focal inflammatory changes are found in between the muscle fibres, but this is more marked in the vascular septa separating the muscles. Here reactions occur around the microfilariae which penetrate into the septa and are found in between the connective tissue fibrils (Plate III Fig 6) and in the walls of the lymphatic vessels. The microfilariae appear in the tissue spaces in fragments and forms which have lost their sheaths and as partly digested forms. Evidence of phagocytosis is shown by the appearance of clusters of microfilarial granules inside the large mononuclear phagocytic cells as well as in more irregular cells resembling the histiocytes. Partly digested microfilariae appear surrounded by empty spaces. The phagocytic vacuolated cells are occasionally found in the lumen of small capillaries, but are more frequent in the walls of the lymphatic vessels. The microfilariae do not seem to penetrate the muscle bundles but are found only in the sheaths Occasionally areas of necrosis in muscle are met with. These lymph vascular reactions are found around the parent worms in the limbs, in the mesentery and at the hila of the lungs. In a lizard which had developed

extensive oedema of one limb there were diffuse inflammatory changes under the skin and accumulation of oedematous fluid under the subcutaneous tissues as well as in muscle. The fluid had coagulated to form pyriform cyst like areas. The condition suggested a secondary infection. In the *heart* of infected lizards the capillary vessels appear distended with groups of microfilariae and the capillary walls beaded. There is also a gradual increase in the supporting tissue of the alveolar walls as in chronic venous congestion. Microfilarial concentration was not met with to any extent in the *liver* and the *spleen* which showed only phagocytic activity to pigment.

Discussion

The study of the developmental forms, the period of maturation of the worm and the time of appearance of microfilariae in the blood in the lizard worms are all of interest since so far we have no accurate data with regard to the human filaria. The close similarity in the morphology of the worms, the developmental stages in the insect vector the habitat in the lymphatic system and the pathological lesions all suggest a similar development for the human worm.

The development of the infective larvae in the deeper lymphatics and their tendency to migrate along the lymphatic vessels to the mesenteric lymphatics are features of some significance. Lane (1937) has suggested that the infective larvae in human filariasis may enter the lymphatic system, the lymph escalator or alternatively the blood escalator From the vascular system they are then supposed to enter the lymphatics of the tissues of predilection such as the testes or the retroperitoneal region. The infective larvae in human filariasis are so large (1,800 × 22μ Menon and Rajamurti 1941) that a passage through the capillary system of the lung is difficult if not improbable unless they make their way through the alveolar walls into the bronchioles as do the ancylostome larvae. In lizard filariasis this experimental study has demonstrated that the lymphatic path is the one that is followed, as the infective larvae (1 000 to 1,250 × 19 to 20μ, in size, Pandit *et al.*, 1929) have not been demonstrated in the lung or in the peripheral blood in any of these animals Forms met with in the hila of the lung were fully developed worms which had presumably migrated from the retroperitoneal lymphatics. In heavy infections such migrating forms could be demonstrated. The tendency for the worm to develop locally has also its parallel in human filariasis where dead or calcified worms are commonly found in the limbs in elephantiasis, while occasionally healthy worms are found in varicose lymphatic vessels or in the glands when they are dissected out.

With regard to the cause of the lymphatic obstruction that is so marked in the lizard there is very little to support a theory of abortion of the worm and discharge of ova, as such ova are much higher up in the uterus, have no distinct

egg shell and have not been found in the lymphatics in any of these cases unless there is mechanical rupture of the worm and displacement by the microtome. The evidence suggests that the obstruction is due to inflammatory changes around the worm This reaction is not only inside the vessel but involves the vessel wall in a chronic lymphangitis. Encapsulating reactions round dead parasites and reactions with coagulum formation around disintegrating parasites have been found in the lizard. The local macrophage reaction in lizard filariasis is minimal in the neighbourhood of healthy worms that have been killed only by fixation, but it is more marked around dead parasites The macrophage reaction and chronic lymphangitis can only be looked upon as due to the products of the worm, after death material that has escaped from the body or to disintegrating microfilariae. The part played by the microfilariae in producing lesions is also significant. Such lesions in the lymphatic system in man have been demonstrated by LANE (1933 1934) The formation of granulomatous nodules has been described in the human spleen by DHAYAGUDE and AMIN (1942) In the lizard disintegrating fragments of the embryos surrounded by macrophages in coagula in the walls of the lymphatic vessels indicate that destruction and phagocytosis take place in the lymphatic system. Such reactions are also well marked in the sheaths of muscle and are followed by fibrous thickening The evidence so far suggests that these reactions play a very important part in producing the obstructive lesions in lizard filariasis. It has not been possible to decide how far hypersensitization is responsible in producing any of these changes. Local necrosis of tissue due to a vascular thrombotic lesion of the Arthus type has not so far been met with The role of secondary infections in exaggerating the obstruction and producing marked lymph oedema is probable in one case with extensive oedema of the fore limb where the histological picture suggested a complicating secondary infection.

The condition of the uterine tubes in all the adult worms examined was identical. All the stages of development of the microfilariae from ovoid cell masses to sausage forms and sheathed coils could be made out in the uterine tubes It may be argued that this is in keeping with the lack of periodicity of the microfilariae, but this can only be settled by a study of the periodic adult worms.

SUMMARY

The course of development of the lizard filaria has been worked out after experimental inoculation of infective larvae into non infected lizards. The different developmental stages of the parasite are fully described. The site of development and the path of the larvae in the lymphatic system suggest analogies to human filariasis. The pathological lesions caused by the parasite are demonstrated and the mechanism of production of the lymphatic obstruction is discussed.

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PORTAL CIRRHOSIS IN IRAQ

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Cirrhosis of the liver is a common disease in Iraq the admissions excluding readmissions, to the Royal Hospital in Baghdad being roughly one-half of those for lobar pneumonia. It is found in infants, children and adults of all ages. In the following, only cases occurring in persons over 14 years of age will be considered because in children the disease differs in certain respects and because the circumstances under which the cases were collected preclude, for statistical reasons, the inclusion of the younger age groups From 136 personally investigated cases of portal cirrhosis, nine have been excluded since they present differences which necessitate their separate consideration. The remaining cases show marked uniformity with respect to course, symptomatology and clinical and laboratory findings. For lack of better terms the larger group will be referred to as atrophic portal cirrhosis and the smaller since the liver was in all cases considerably enlarged hypertrophic portal cirrhosis. This latter term is not meant to imply any relationship with any other disease to which this name has been applied.

Atrophic Portal Cirrhosis

This is a disease of the poorest classes and is largely though not exclusively found among persons working on the land. Out of ninety-three cases, sixty-five were fellaheen (70 per cent.) The remainder were small shopkeepers, labourers brickmakers, mudworkers, pedlars of a social standing barely above the fellaheen, and in only two cases could the patients be said to be moderately well to-do

Patients from all parts and of all races in Iraq are represented, but on the basis of figures from this hospital no definite conclusion as to local incidence can be given it is most striking that few patients came from large towns.

The disease is very much more common among men than women, though figures would be misleading since women are less likely to present themselves at hospitals.

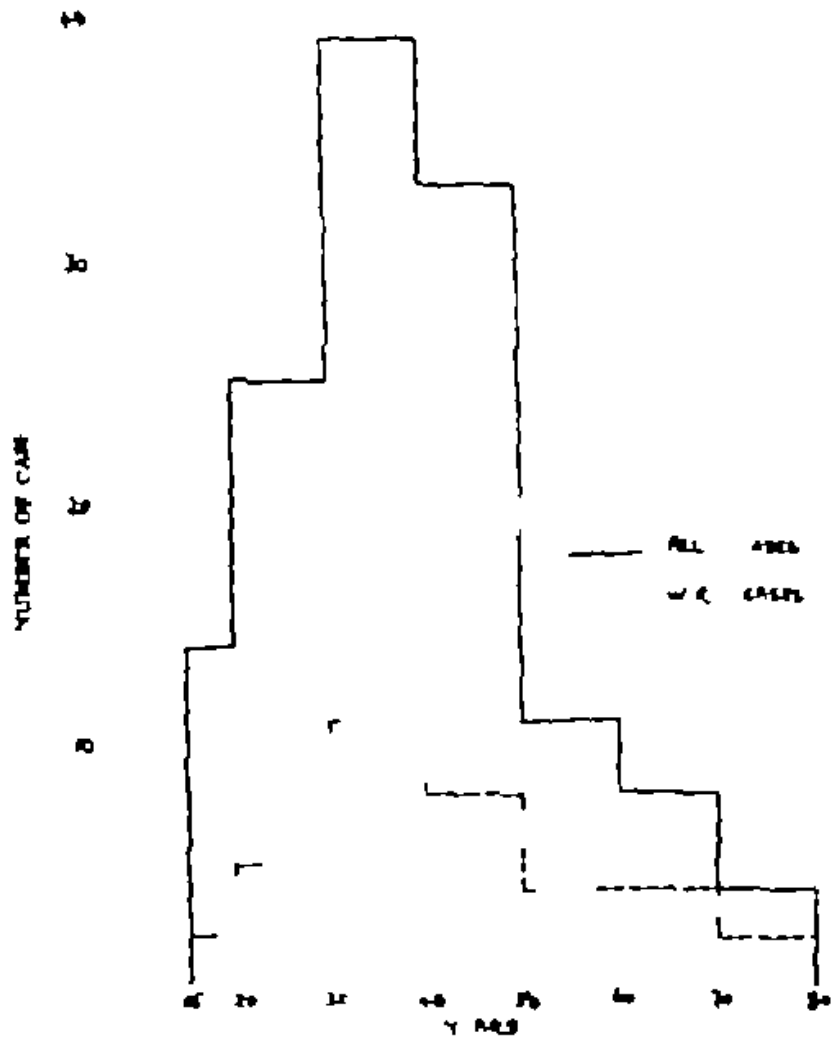
No instance of more than one case occurring in a family has been met with.

The majority of the cases are in the 3rd, 4th and 5th decades (Graph) the maximum incidence being in the 4th. The average age was 36·2 years.

GRAPH

AGE DISTRIBUTION OF CASES OF PORTAL CIRRHOSIS.

Note.—The number of cases in the age group 15 to 20 has been doubled as it is only a 5-year period



The suddenness of the decline after the age of 50 may be partly attributable to the relatively short span of life in Iraq. There is no difference in the nature of the disease in adult patients of different ages.

Early Course of the Disease.—Treatment is rarely sought until the accumulation of ascitic fluid prevents work, so that the early stages are not often seen. The patient dates the commencement of his illness from the beginning of

abdominal distension this is usually about a month before he is first seen but varies from 10 days to 5 months. In most cases fever sometimes accompanied by chills was experienced just before the distension was noticed but no other early symptoms were reported.

Ascites and Oedema.—Once ascites has formed, regular tappings of the abdomen every 2 or 3 weeks are needed to avoid gross discomfort and dyspnoea and these have to be continued until shortly before death. ROLLESTON and MCNEE (1929) state that tapping is seldom needed more than 2 or 3 times but most cases of cirrhosis in Iraq survive many more than this and the number may reach 40 or 50. A few cases have been met with in which ascites necessitating repeated tapping disappeared entirely enabling the patient to return to his work. After an interval, in one case of two years, the ascites returned. This is probably due to the formation of a temporarily efficient collateral circulation.

Oedema usually appears first in the feet soon after the development of ascites and spreads to the thighs, scrotum, anterior abdominal wall and back but occasionally oedema precedes abdominal distension. In this series 63 per cent. of the cases were oedematous. The usual explanation of the oedema is that it is caused by compression of abdominal veins and in many cases this is confirmed by its improvement after paracentesis. That this explanation is not adequate in all cases is shown by the following:—

(*a*) Occasionally oedema precedes abdominal distension.

(*b*) The degree of oedema does not always correspond to the abdominal tension nor is it always relieved by repeated tapping.

(*c*) The oedema is often found to extend further up the back than can be explained by compression of abdominal veins and has been detected in the anterior thoracic wall.

(*d*) Venous engorgement with the appearance of dilated veins forming a collateral circulation is rare.

In such cases oedema formation is due to a disturbance in the plasma proteins through liver damage leading to a lowering of the plasma osmotic pressure.

In the last stages of the disease ascites and oedema accumulate less rapidly tapping can be postponed for longer and longer intervals and in many cases at death oedema has disappeared completely.

Wasting.—In the early stages, wasting though present, is not marked but increases steadily until extreme emaciation is reached and the face becomes drawn and thin. The bloated face with dilated veins common in alcoholic cirrhosis is not seen.

Liver.—This was palpable below the costal margin in the mid-clavicular line in only 7 per cent. of the cases. No evidence that a large cirrhotic liver exists at any stage of the disease was found. The average weight at autopsy was 1 063 grammes. This gives a false impression of the size of the liver as the specific gravity is above normal.

Spleen.—This was palpable in 65 per cent. of the cases and was always found to be enlarged at autopsy. Among a population in which malaria is endemic, much of this enlargement must be due to chronic malaria. The spleen is hard, with a well-marked notch and not tender. Discomfort in its neighbourhood is often felt and many patients suffer at some time from severe attacks of pain under the left costal margin usually associated with a rise in temperature. At these times a rub can sometimes be heard or friction felt. Once the patient has come under observation a further change in size does not occur nor does the size of the spleen bear any relation to the duration of the disease or to its stage or prognosis. The average weight of the spleen at autopsy was 826 grammes and there was no relationship between the weight of the liver and spleen.

Jaundice.—In none of the cases was a history of jaundice given and in only 12 per cent. was there definite tinting of the sclera. This however is difficult to detect as the sclera is usually pigmented through previous conjunctivitis, medication or exposure. Fouchet's reaction on the serum was negative in 50 per cent. of the cases and strongly positive in 20 per cent. When positive, the van den Bergh reaction was a weak direct one.

Fever.—The course of the disease once ascites has developed, is for the most part afebrile but many patients have short periods of fever lasting from a few days to 2 or 3 weeks. The temperature rarely rises above 38·5° C. and may be associated with pain over the spleen.

Haemorrhage.—Haematemesis occurred in one case only preceding by 2 weeks the development of ascites. Occasionally petechial haemorrhages are seen but there seems to be no special tendency towards epistaxis or rectal haemorrhage. The platelet count is generally reduced.

Gastro-intestinal Symptoms.—There is often a little epigastric discomfort but definite dyspepsia, vomiting, diarrhoea or constipation are not symptoms of the disease.

Urine.—This is small in volume, highly coloured, acid in reaction and precipitates urates on standing. When the abdomen is tightly distended traces of albumin are often present.

Wassermann Reaction.

This was positive in 29·8 per cent. of the cases (compared with 17·8 per cent. in 500 consecutive non-cirrhotic cases admitted to the hospital). There was a history of syphilis in 3 per cent. of the cases but it is a matter of extreme difficulty to get an adequate history from the patients. In none was there any other evidence of syphilis. The symptoms, age distribution (Graph), physical signs and course of the disease were the same in the Wassermann positive and negative cases. Oedema was equally common in the two groups but splenic enlargement was slightly more common and a positive Fouchet reaction much more common, when the Wassermann reaction was positive (Table I).

TABLE I

	W.R. negative.	W.R. positive
Average age	37 years	37 years
Percentage with oedema ..	60	60
Percentage with splenic enlargement	61	72
Percentage with positive Fouchet	38	63

Improvement on antisyphilitic treatment (iodides mercury and bismuth) occurred in one case only though it was tried in all the Wassermann positive cases. This single case could not be observed over a long enough period to decide if the improvement was maintained. The significance of the positive Wassermann is questionable. Four possibilities present themselves —

(*a*) *Syphilis is coincidental* —This is unlikely as the proportion of the cases with a positive Wassermann is considerably larger than in the rest of the population.

(*b*) *All cases are syphilitic but a positive Wassermann is only found in some* — If this were true more evidence of syphilitic infection would have been found in previous and in family histories.

(*c*) *A positive Wassermann does not always indicate syphilis in these cases* — Yaws and relapsing fever which may cause positive reactions, do not occur in Iraq. At one time it seemed established that malaria rarely led to a positive reaction (IYENGER 1920, JOHNSON 1921, DOWNS 1922, LLOYD and BAHADUR, 1926, SAUNDERS and TURNER, 1935) but more recent work by GREVEL, SEN GUPTA and DAS (1938) on malarial patients in India and by KITCHEN, WEBB and KUPPER (1939) and BURNEY, MAYS and IKKRANT (1942) on inoculated malaria has led to a reversion to the opinion of early workers that a positive Wassermann reaction is likely to be met with in non-syphilitic patients during the febrile period and up to 4 weeks after its termination. In Iraq another important condition giving a positive Wassermann and caused by a *Treponema* morphologically identical with *T. pallidum* is the non-venereal disease bejel. This is widely distributed throughout the country and the lesions, often contracted in childhood are unlikely to be referred to by the patient. In tuberculosis, false positive reactions occur with extreme rarity if at all, when a satisfactory technique is used (KILDUFFE, 1931, DOWNS 1922). CARDON (1942) has pointed out the association of false positive reactions with diseases in which there is hyperproteinaemia and hyperglobulinaemia. In cirrhosis of the liver hyperproteinaemia does not occur but the serum globulin is usually above normal. In twenty of the present series the globulin was estimated but the findings did not bear out the suggestion that positive Wassermann reactions could be explained in this way. From these considerations it is apparent that, on account of malaria and bejel, syphilis is less common in association with cirrhosis than the percentage of positive Wassermann reactions would suggest.

(*d*) *Syphilis plays some part in the causation of the disease in some of the cases*.—This has been maintained frequently in the past for portal cirrhosis in other parts of the world, *e.g.*, by SYMMERS (1916), LETULLE (1918), and more recently by SCHUMACHER (1942).

On the evidence available here no final conclusion can be reached but if syphilis plays any part in the aetiology of the disease in Iraq it must be a subsidiary one since it does not occur in all cases and in those in which it does occur the symptoms are modified in details only.

Formol Reaction

One drop 40 per cent. formol was added to 0·5 ml. serum in a small test-tube. Normal serum remains unchanged. When changes develop they are of two kinds: (*a*) the serum becomes cloudy, this may increase until it is quite opaque; (*b*) the serum may form a jelly. These changes may progress for 24 hours but after that no further changes take place. Since the serum only becomes opaque when a firm jelly is formed and intermediate changes in opalescence are difficult to judge when the serum is lipaemic it was found that results could best be assessed on gel formation only. The serum was examined after 24 hours and three stages distinguished: (1) the serum remains liquid—negative reaction, (2) the serum is semi-solid, *i.e.*, it cannot be poured from the tube but it is not a firm jelly—weak positive reaction, (3) the serum has formed a firm jelly—strong positive reaction.

In this series of cases the results were as follows: negative, 11 per cent.; weak positive, 21 per cent.; and strong positive 68 per cent.

Serum Euglobulin.

Method: The euglobulin was precipitated with 14 per cent. sodium sulphate and the tyrosine equivalent of the precipitated euglobulin estimated by Folin's phenol reagent (PEOPLES and WARWICK, 1939).

0·2 ml. serum was added to 6 ml. 14 per cent. sodium sulphate in a conical centrifuge tube and allowed to stand in an incubator at 37° C. for at least 3 hours. The solution was then centrifuged till clear, the supernatant fluid poured off and the precipitate washed twice with 5 ml. portions of 14 per cent. sodium sulphate solution. The euglobulin was then dissolved in 4·5 ml. water, 0·5 ml. 5% sodium hydroxide solution added and allowed to stand in boiling water for 10 minutes. A standard was prepared in a 25 ml. cylinder containing 2 ml. standard tyrosine solution (0·2 grammes tyrosine in 1,000 ml. N/10 hydrochloric acid), 20·5 ml. water and 1 ml. 5% sodium hydroxide solution. The standard and the unknown were cooled to the same temperature in cold water and 0·3 ml. Folin's phenol reagent added to the unknown and 1·5 ml. to the standard. The volume of the unknown was made up to 5 ml. and after thorough mixing the colours were compared in a colorimeter. The calibration curve over the range of normal and pathological sera is not a straight line and curve must be constructed by using standard solutions of different strengths from which the tyrosine equivalent of the precipitated euglobulin may be read. The figures given below represent therefore the mg. tyrosine per 100 ml. colorimetrically equivalent to the euglobulin in 100 ml. serum.

Table II records the results obtained in seventy-six cases of portal cirrhosis and forty three control cases in which there was no evidence of any disease involving liver or spleen nor any condition such as severe anaemia or nephritis which might lead to a disturbance of the serum proteins. It will be seen that, whereas in the control group the euglobulin, expressed in terms of tyrosine, was below 80 in 95 per cent. of cases, it was above this value in 96 per cent. of cases of portal cirrhosis.

TABLE II

Serum euglobulin-tyrosine value	Normal		Cirrhosis	
	Number of cases.	Percentage.	Number of cases.	Percentage
0–20	10	23 2		
21–40	20	46 5		
41–60	11	25·6	3	4·0
61–80	2	4 7	10	13 1
81–100			10	13 1
101–120			10	13 1
121–140			11	14 5
141–160			10	13 1
161–180			12	15 8
181–200			3	4·0
201–220			5	6 6
221–240			2	2·6

The serum euglobulin is raised in other conditions, *e g* in malaria, acute yellow atrophy kala azar some cases of catarrhal jaundice amoebic hepatitis and hepatic enlargement due to cardiac failure so that the diagnostic value of the test is limited. Until further information has been accumulated as to the conditions leading to a rise in serum euglobulin, it can only be said that any case of ascites having a normal euglobulin is unlikely to be one of portal cirrhosis The test has been found useful in differentiating such conditions as tuberculous peritonitis, abdominal carcinomatosis and hydatid disease of the peritoneum.

It has been suggested by RAY (1924) BRAHMACHARI (1923), and GANGULI (1925) that the formol reaction depends on an increase in the serum euglobulin A comparison of the serum euglobulin and the results of the formol reaction (Table III) shows that when the euglobulin is below 60 the formol reaction is negative, above 180 it is strongly positive while for intermediate values it may be negative, weakly positive or strongly positive. There is therefore a rough

TABLE III

	Serum euglobulin-tyrosine value			
Formol reaction	0–60	60–120	120–180	180–240
Negative	100%	13 %	3 %	0%
Weak positive	0	30 %	23%	0%
Strong positive	0 %	57 %	74%	100 %

correlation but the figures indicate that some other factor apart from the percentage of euglobulin, must be involved.

HISTOLOGY

Numerous sections of liver and spleen examined from autopsy material showed the usual sequence of pathological changes associated with progressive atrophic portal cirrhosis and no distinctive features worthy of special note have been observed in this series of cases. Neither living nor degenerate ova of *Schistosoma haematobium* have been found in any of the sections examined and methods of digestion and concentration have likewise yielded negative results. Special attention has been directed to the detection of haemozoin as indicating a latent or past malarial infection. The presence of haemozoin in liver or spleen was a rare finding pointing to the fact that malaria plays no important part in the causation of this condition.

TABLE IV

COMPARISON OF PORTAL CIRRHOSIS IN WESTERN COUNTRIES AND IN IRAQ

	Western Countries	Iraq
Average age	A disease of late middle life Alcoholic 44·6 years. Non-alcoholic 49·8 years (ROLLESTON and McNEE, 1929). 51·2 years (SCHMINCKE, 1937).	A disease of early middle life. 36 years.
Sex	Male more than female.	
Heredity	Does not run in families.	
Occupation	More often seen in those whose life is sedentary than in those leading an active outdoor life (ROLLESTON and McNEE, 1929). Rare in upper and well-to-do classes (DUCKWORTH, 1874)	Principally in farm labourers. Rare in upper classes.
Course of disease and appearance of patient	In general the same. Fever not common	Fever common.
Liver Weight of liver	Similar morbid anatomy and histology 1,780 grammes (ROLLESTON and McNEE, 1929). 1,364 grammes (ELKIN and GRAY 1933).	1,063 grammes.

TABLE IV—*continued*

	WESTERN COUNTRIES.	IRAQ
Spleen. Weight of spleen	Similar morbid anatomy and histology 313 grammes (ROLLESTON and McNEE, 1929).	836 grammes
Jaundice.	¼–½ cases (ROLLESTON and McNEE)	12% cases, but difficult to assess on account of pigmentation. Fouchet negative in 50%
Ascites	85% cases dying of cirrhosis but more common with a comparatively small than with a large cirrhotic liver	Almost invariable.
Oedema	75% cases.	63% cases
Dyspepsia.	Common.	Not common.
Clubbing of fingers.	Rare	
Urine	Small in quantity and highly pigmented no glycosuria.	
Average duration after first tapping	46 days	Considerably longer
Positive W.R.	Figures very enormously CATES (1941) 10% EVANS and GRAY (1935) 15% SCHUMACHER (1937) 27% LETULLE (1918) OWEN (1921), CHAUFFORD and BRODIN (1924) 40–45% SYMMERS (1916) 80%	30% cases.
Cause of death.	Progressive weakness and coma with intercurrent infection. Gastro-intestinal haemorrhage. 20% (EVANS and GRAY 1935) 31% (CATES, 1941)	Progressive weakness and coma with intercurrent infection of which bronchopneumonia is the most common. Haemorrhage is a very uncommon cause of death.

AETIOLOGY

Diet

Of the many factors which have been advanced as concerned in the actiology of portal cirrhosis alcohol, in western countries is one of the most important.

In the present series all but a very few of the patients had never taken alcohol and only one had consumed it regularly Its consumption is prevented by religion, custom and expense and it can therefore be excluded as a cause of cirrhosis in the cases considered here.

Hot spices, which have been suggested as a cause in India, are not taken *to any considerable extent in Iraq* Red pepper is the only one used.

An inquiry into the diets of the class of patient among which cirrhosis is common shows it to consist mainly of carbohydrates (wheat barley rice and dates), vegetables and fruits. It is remarkably deficient in animal protein, meat rarely being eaten and then only in small quantities on account of expense. Avitaminoses are not common in Iraq and no particular vitamin deficiency condition has been found associated with it

Intestinal Parasites

The commonest intestinal parasites in Iraq are *Ankylostoma duodenale Ascaris lumbricoides* and *Entamoeba histolytica*. In Table V the incidence of infestation with these parasites in the cases of portal cirrhosis is compared with that of a series of 1 000 apparently healthy persons in Iraq investigated by SHEREKJI BOSWELL and BEATTIE (1939)

TABLE V

	Cirrhosis.	Normal.
Ankylostoma duodenale	18%	25·6%
Ascaris lumbricoides	1	13·6%
Entamoeba histolytica ...	0%	22·8%

Malaria

This has been said to be a cause of cirrhosis in India (SIVERN 1923 HUGHES, 1933) and in Syria (YENIKOMSHIAN 1934) and is endemic throughout the areas from which the patients come. A history of malaria cannot usually be distinguished from other causes of fever None of the patients were actually suffering from malaria and it is not common to find evidence of malaria at postmortem. A number of patients were given intravenous injections of adrenaline and although this often caused a rise in temperature it did not lead to typical malarial attacks nor to the appearance of malarial parasites in the blood.

Bilharziasis.

S mansoni has been shown in Egypt by DAY (1924) to lead to cirrhosis of the liver The form found in Iraq is *S haematobium S mansoni* being extremely rare and only found in imported cases. In the present series there were four

cases with urinary bilharziasis. Sections of liver and spleen never revealed the presence of infection.

Kala-azar

This does not occur in Iraq. Dermal leishmaniasis is common in some parts of the country but the majority of the present cases come from areas where it is not found.

Syphilis was discussed above and may sometimes be a contributory factor.

Such a survey of the possible aetiology yields only one factor common to all cases, namely poverty. This leads to a poor and restricted diet, the deficiency being principally in animal protein. Papers on portal cirrhosis in eastern countries frequently contain references to the poverty in first-class protein of the diets of those affected, *e.g.* RADHAKRISHNA RAO (1933) and YENIKOMSHIAN (1934). ELMAN and HEIFETZ (1942) have produced changes in the livers of animals kept on a protein deficient diet and MILLER and WHIPPLE (1942) have shown that such animals are particularly susceptible to liver poisons. While the literature of portal cirrhosis is full of examples of the fallacy of drawing conclusions of its aetiology from animal experiments, such experiments can be used as circumstantial evidence. It is therefore suggested that cirrhosis of the liver in Iraq is caused by a protein deficiency in the diet resulting in a liver which can be damaged by toxic substances which normally would not damage it. Malaria, syphilis and intestinal parasites are possible sources of such toxins but there are many others and different toxins probably act in different cases. Chronic alcoholism, so often associated with portal cirrhosis in Europe and America, by leading to a decreased intake of food (ROMANO 1937) and by interfering with absorption may play a role in the development of cirrhosis of the liver similar to its role in alcoholic neuritis, namely by leading to a deficiency condition. This would explain the difficulty experienced by many workers in producing cirrhosis in animals by the administration of alcohol and also the similarity of the disease to portal cirrhosis in Iraq.

SUMMARY

1. A description of the portal cirrhosis of Iraq based on 136 cases, is given.
2. The condition is compared with the portal cirrhosis of western countries. The main differences are in the age incidence, the occupation of the patients, the size of the liver and spleen, the rareness of haemorrhage and the fact that alcohol plays no part in the aetiology.
3. A positive formol reaction was obtained in 89 per cent. of the cases.
4. The serum euglobulin was raised in 95 per cent. of the cases.
5. The value and limitations of the formol reaction and serum euglobulin estimation in differential diagnosis are indicated.

6. The aetiology is discussed and the conclusion reached that portal cirrhosis in Iraq is due to a dietetic protein deficiency resulting in a liver less resistant to toxins than normally. The possible sources of such toxins is indicated.

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LOBAR PNEUMONIA IN AFRICAN SOLDIERS

BY

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Whilst in West Africa I studied a series of cases of pneumococcal lobar pneumonia which included a type V outbreak. The patients all African natives were mostly recent recruits.

One assumed that natives were especially prone to succumb to lobar pneumonia (an assumption which later had to be modified) and hence they seemed ideal subjects for the evaluation of sulphapyridine therapy

The period covered was from November 1941 to July 1942 when 159 cases of pneumococcal lobar pneumonia and 66 of atypical pneumonia* were observed. The incidence of respiratory conditions which formed 30 to 40 per cent. of the total admissions to the Medical Division of the hospital is shown in Table I

The sputum was examined by direct smear and if pneumococci were present in overwhelming numbers I typed them at once if not, the sputum was plated and the predominant organism isolated We were not able to do mouse inoculation nor any elaborate bacteriological investigation, and so cases of doubt were

* I use the term atypical as proposed by Cole to designate all forms of pneumonia which do not conform clinically with typical lobar pneumonia It is to be clearly understood that virus pneumonia is not referred to

excluded. In any study of pneumonia blood cultures should be done, but this was found to be impracticable. In complicated cases, or those not responding to sulphapyridine therapy radiological examination was carried out. Nursing was done under excellent conditions by native orderlies under the supervision of a European sister. Patients remained in bed only as long as they desired. Food was abundant, of the customary native kind, and the daily intake of sodium chloride was found to be approximately 10 grammes.

TABLE I

MONTHLY DISTRIBUTION OF RESPIRATORY CONDITIONS.

	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	June
Lobar pneumonia	15	11	7	10	18	21	33	23
Atypical pneumonia	4	4	3	4	7	17	15	1
Pleurisy	0	1	0	0	1	3	14	6
Primary pleural effusion	1	0	0	0	1	1	3	4
Acute bronchitis	3	1	1	1	3	3	11	14
Chronic bronchitis	2	0		1	1	2	3	2
Pulmonary tuberculosis		0	0	1	1	0	0	1
Asthma	1	0	1	0	0	0	0	0

I divided the cases into two main groups those receiving sulphapyridine from the outset and those not so doing. Only if the cases in the latter group became sufficiently ill to make the administration of the drug imperative, was it given. These three groups will be referred to as "Sulphapyridine from the onset," "Sulphapyridine delayed" and "No sulphapyridine." The gravity of the patient's condition on admission determined whether or not he received specific drug therapy at once.

GENERAL CONSIDERATIONS

Reaction to pneumonia.—Two main types of native were admitted, the so-called educated and the uneducated. The latter judged illness by four symptoms—pain, fever, headache and constipation. Cough and sputum were not often complained of and dyspnoea never. I have no doubt that the native was more susceptible to pneumonia and I was often amazed at the rapid way in which the uneducated ones recovered. When their temperature was normal they were ready to get up and return to work, even though the lung was still solid (MACNAUGHT and MURRAY LYON 1943). The educated natives on the other hand often made the plea of "I never be fit for work." I did not see any deleterious effect in allowing them to do as they pleased, although I never permitted them to return to work until fit. However on their discharge from hospital they resumed full duty.

Mode of spread.—It was found that proximity was of no significance in the outbreak of type V pneumonia as cases arose in different places and in different camps at the same time.

Age.—The native rarely knew his age but all were under 40 and the majority between 20 and 30 years of age.

Diagnosis.—Lobar pneumonia was diagnosed in ninety-one cases on the day of admission, in twenty-three after 1 day seventeen after 2 days, eighteen after 3 days, two after 4 days, four after 5 days three after 6 days and one on the 7th day.

Lobes involved.—The parts involved were right lower lobe in seventy two left lower lobe in eighty left upper lobe in six, and right upper zone in thirty, *i.e.* right lung in 102 and left lung in 86 cases. As X-rays were not always available I could not differentiate lobar involvement further.

Crisis.—The crisis occurred on an average on the 8th day of illness in the non sulphapyridine group and lysis was seen in fifteen cases.

The period of stay in hospital of these cases of lobar pneumonia was 19 to 23 days.

Complications

The complications are listed in Table II. There were eight deaths three of which were directly attributable to the pneumonia.

Pericarditis.—Two cases of purulent pericarditis were seen, one a type I infection, also complicated by a lung abscess (postmortem finding) who died, and the other untyped who lived. Both received sulphapyridine from the onset.

TABLE II

COMPLICATIONS

	Malaria and filariasis	Jaundice	Effusion	Empyema	Pericarditis	Meningitis	Monin ghamia	Peritonitis	Abscess	Total	Dead
Sulphapyridine from the onset	0	2	1	3	*	~	*	–	1	41	4
Sulphapyridine delayed	1	16	4	–	–	1	–	1	–	4	1
No sulphapyridine	*	6	*	1	–	–	–	1	–	71	3

Other Complications. Herpes 1. Toxic psychosis 1. Encephalitis 1. Heart failure 1. Partial atelectasis 2. Arthritis 4.

The patient, aged 35 years, who lived, had a pneumococcal pneumonia of the left lower lobe, which did not react to drug therapy lysis occurring after 15 days. Eighteen days after admission he was screened and found to have a large pericardial effusion. This was tapped and 5 c.c. of purulent fluid obtained, which on culture yielded a pure growth of pneumococci. He improved steadily refused to stay in bed, and returned to his unit 38 days after admission. There were no abnormal signs in the lungs. Seen 6 weeks later he was quite well and clinically and radiologically there were no signs of pericardial fluid.

Meningitis.—The patient who died in the delayed group had meningitis and peritonitis, the result of a type I pneumococcal infection.

Peritonitis.—The man who died in the "No sulphapyridine" group had at autopsy a resolving right basal pneumonia subdiaphragmatic plastic peritonitis and advanced cirrhosis of the liver. The cirrhosis largely contributed to his death. The pneumococcus was not typed.

Heart failure.—This complication was seen in a patient who succumbed to type XII infection. Autopsy was not performed.

Encephalitis.—The patient was admitted in coma and death occurred within 24 hours. Autopsy revealed red hepatization of the right middle and lower lobes and a flabby brain showing numerous punctate haemorrhages (pneumococci were not recovered from the brain substance).

Malaria and filariasis.—Blood films were taken in cases where the temperature remained high or showed unexpected rises. In those cases where malarial parasites were found intramuscular quinine was given. The response was not always as good as in uncomplicated malaria. No treatment was used for filariasis, and I found that malaria and filariasis did not seem to have any deleterious effect on the pneumonia.

Partial atelectasis and herpes.—These complications were seen in type V cases.

Delayed resolution is commented on under sulphapyridine.

Types.

From November to March none of the forty three cases was typed as serum was not available but from March to July all but nineteen were typed, with the results shown in Table III. I cannot agree with *Joules* (1943) that the pneumococcus disappears from the sputum following small doses of sulphonamide drugs as I successfully retyped many cases after sulphapyridine had been given.

The interesting feature was the occurrence of odd types and untypable strains prior to the outbreak of type V in May. There were two cases whose sputum, packed with pneumococci, reacted to Group A serum, but not to any of the types contained in that group. Were these new types of pneumococci? The atypical pneumonias were prevalent up to May and then most assumed the lobar form and of a type V too. The soil was the same. Had the pneumo-

TABLE III

TYPES OF PNEUMOCOCCI

	Not typed	Friedlander	No sputum	Untypable	Types																Total
				Serum Groups																	
				A	E	?	1	2	3	4	5	7	8	9	12	13	20	21	24	28	29	
March	12	1	–				2		2		1		1									19
April	2		1	2		5		1			5	1		1			1	1	1		1	21
May	3		5		1				1	1	41				1							53
June	2		2		1			1			12	1	1			2				1		23

coccus so increased its virulence (for these cases were more severe clinically) and altered its character that it was now able to invade one and all and in a lobar form? (In this regard it is interesting to note that type II which is immunologically related to type V was not prevalent.)

Type V cases.—There were no deaths and the complications are set out below

TABLE IV

TYPE V COMPLICATIONS.

	Total	Malaria and filariasis	Jaundice	Pleural effusion	Empyema	Menin gismus	Herpes	Delayed resolution	Arthritis	Partial atelectasis
Sulphapyridine *ab initio*	6	1	—	—	1	—	—	—	—	—
Sulphapyridine delayed	22	—	6	2	—	1	—	—	2	1
No sulphapyridine	31	2	5	2	2	—	1	4	1	1

We had a susceptible subject the native and a pneumococcus which had presumably reached its height of virulence from passage as evidenced by the sudden outbreak of type V cases yet it did not carry the mortality and complications usually associated with it in spite of the fact that a minority received sulphapyridine immediately (REIMANN 1938)

It will be noticed that delayed resolution as judged clinically occurred in the "no treatment" group and *not* in the sulphapyridine group

SULPHAPYRIDINE.

The average total of sulphapyridine given was 20 grammes 2 grammes at once, followed in 2 hours by 1 gramme 4 hourly and thereafter until the temperature was normal, when the dose was gradually reduced to 1½ grammes daily

It was found that irrespective of the day of illness on which the drug was commenced a prompt reaction could be expected in 50 to 60 per cent. of cases and in over 80 per cent. the temperature was normal in 2 days. A prompt reaction was one in which the temperature fell to normal in 24 hours and thereafter remained so, unless complications supervened. There was no response to the drug in six cases.

Macroscopic haematuria was not seen, vomiting was a rare feature (eight cases) and the drug had never to be discontinued because of it.

The chest was clear clinically in the treated and untreated groups on approximately the 15th day after admission (this excepts complicated cases), and I could find no evidence to indicate that sulphapyridine administration delayed lung resolution or led to unresolved pneumonia. On the contrary the number of cases which did not show clearing was greater in the untreated group (eleven as against seven in each of the treated groups) and on reference to Table II it will be seen that in these the complications were fewer

Non-reactors to sulphapyridine.—I was especially interested in the cases that did not respond to sulphapyridine therapy even though the sputum contained pneumococci and there were no obvious complications (cf. MOORE *et al.*, 1941) There were six such cases. Two developed fatal complications, meningitis and pericarditis in spite of drug therapy Both were type I infections. Another patient had an unsuspected small pleural effusion, and I found that in the presence of fluid sulphapyridine was ineffective as judged by the temperature response. Two other cases had a partial atelectasis of the involved lobe of the lung which was obscured and only became evident radiologically as resolution was taking place. In the remaining case there was an underlying tuberculous lesion and since return to this country I have again seen this complication. These two cases I will describe in more detail.

CASES

An African soldier aged [illegible] years was admitted on 18.5.41, with a type V pneumonia. There was no response to sulphapyridine therapy and radiological examination showed consolidation of the right upper lobe The temperature returned to normal by lysis 20 days after admission. Repeated radiological examination showed clearing of the opacity which was never complete but there was never any evidence of cavitation. Repeated sputum examination was carried out and on 28.7.42 tubercle bacilli were found. His general condition was good and he had gained weight. Here there was undoubtedly an underlying tubercular lesion which had been reactivated by a type V lobar pneumonia.

This would account for the non-reaction to sulphapyridine and the persistence of the clinical and radiological signs

A boy A. C. aged 15 years was admitted to a Military Hospital in England on 19 7 43 with a 4 days history of dry cough pleuritic pain in the right lower chest, and shivering The temperature was 102 F and there were signs of consolidation at the right base The pneumococcus was not typed. No response to sulphapyridine was obtained and on 2.8 43 attempted aspiration was negative. He was labelled unresolved pneumonia. I saw him on 9 8 43 when clinically there were signs of lobar involvement at the right base and a few moist sounds in the left mid-zone posteriorly Radiological examination revealed a diffuse opacity in the right lower lobe, clearing in patches and mottling in the left mid zone upper zones clear The sputum was packed with pneumococci and tubercle bacilli were found in it on direct smear on 14 8 43 In this case there was probably an old tuberculous basal lesion, maybe a Ghon's focus, reactivated by a lobar pneumonia and I have no doubt that the left mid zone lesion was a tuberculous spread.

Other Interesting Cases

Staphylococcal Pneumonia —I saw two cases neither of which showed any reaction to specific drug therapy and both showed lung cavitation one at autopsy The one that recovered had a 4 days history of pain in the right upper chest, and X ray revealed a cavity at the right apex which 17 days later was very large and showed a fluid level. Twenty six days later the radiograph showed a very small cavity no fluid level and little surrounding pneumonitis (cf REIMANN 1933) Sputum was persistently negative for tubercle bacilli.

B pyocyaneus Pneumonia.—The patient, aged 28 years gave a reliable history One day prior to admission, 24 4 42, he complained of the sudden onset of cough, right basal pleuritic pain, headache fever and the coughing up of almost pure blood. On examination he was acutely ill temperature 104° F with marked cyanosis and dyspnoea, and sputum consisting of bright red blood. The signs in the chest indicated scattered consolidation at the right base, not of lobar distribution. The sputum did not contain pneumococci but *B pyocyaneus* in pure culture—repeatedly confirmed. He was given sulphapyridine and the temperature fell critically with a corresponding fall in the pulse rate and some improvement in the general condition. Sulphapyridine was continued for 4 days The signs in the chest did not alter and the sputum, although less was almost pure blood. On 1.5 42 he complained of intense aching in the bones of the legs, and 3 days later his temperature rose suddenly from normal to 104 F with a corresponding rise in pulse rate, and increase of bloody sputum. Two days later the right lower lobe was solid and the temperature normal—sulphapyridine had not been given. Lung puncture was performed and *B pyocyaneus* grown. Screening on 28 5 42 showed an incompletely resolved pneumonia of the right lower lobe and no fluid. He was apyrexial and his general condition excellent.

Crisis

Another point which I investigated was whether the crisis induced by sulphapyridine corresponded to the normal crisis. One has heard of and encountered cases of unresolved lobar pneumonia said to be due to sulphapyridine therapy that have made one wonder if the drug cuts short the antibody mechanism which comes into play at the time of the crisis (WELSLEY and SPINK, 1942) Does the bacteriostasis produced by sulphapyridine prevent the normal reaction of the host to the pneumococcus? We know that in lobar pneumonia the chloride excretion is almost completely suppressed at the time that hepatization takes place in the lung being resumed again 1 or 2 days after the crisis (HUTCHINSON 1898) The daily urinary chloride output was measured in twelve cases of pneumococcal lobar pneumonia receiving no sulphapyridine and in a similar number having the drug for some days before and after the

crisis, whilst the sodium chloride intake remained constant at 10 grammes daily. The urinary chloride was determined by the method of HARVEY (1910). It was found that the urinary chloride output was resumed at approximately the same interval after the crisis irrespective of whether it was natural or sulphapyridine induced. Does this mean that the natural crisis in lobar pneumonia is due to bacteriostasis of the pneumococcus? This would not seem improbable as the antibodies appear to be in maximum concentration at the time of the crisis.

DISCUSSION

This study was interesting as one followed different types of pneumococci producing lobar and atypical pictures to the ultimate outbreak of a type V lobar pneumonia. It would almost seem as though the pneumococcus had prepared itself for the final assault, yet the latter did not produce the fatalities or complications one would have expected (FINLAND quoted by REIMANN 1938)—they were left to type I. This mildness was unexpected in so far as these natives, unlike ourselves, probably lacked previous exposure and the development of a specific immunity to infection. However it is not surprising and only serves to emphasize the fact that the same type of pneumococcus varies in the effects it produces from year to year.

The vast majority of cases recovered in spite of sulphapyridine therapy and even though cases were left until they had to have specific drug therapy the mortality, complications and response to the drug were not altered. The low mortality in the severely ill or sulphapyridine from the onset group was undoubtedly due to the drug. Lack of response to sulphapyridine therapy in pneumococcal pneumonia should make one think of the complications outlined above (cf. MOORE *et al* 1941) and in these cases no good purpose is served in continuing the drug. I would go so far as to say that if no response as judged by the temperature chart is obtained in 48 hours, the drug should be discontinued.

With the advent of specific drug therapy nursing is apt to be neglected, and in my series of cases I have not the slightest doubt that nursing was an important factor in the low mortality encountered, since this was probably the first time these natives had had the benefit of hospital treatment. Another therapeutic weapon often overlooked and misused is the use of oxygen (STANSON 1936). Specific drug therapy has by no means written the final word in the treatment of lobar pneumonia (ANDERSON 1943).

The native's reaction to disease was extremely interesting. He had none of the burdens of modern civilization and I felt, as did the sisters, that time and again he recovered where a European with the same extent and severity of disease would have succumbed. He was either well or ill—there was no half-way house, and if well then he was fit for work. I cannot help feeling that we would be better able to withstand disease were we of the same mind.

SUMMARY

The symptomatology pneumococcal types and complications were studied in 159 cases of lobar pneumonia in African soldiers eight of whom died. Included in this group were fifty nine cases of type V lobar pneumonia who all recovered with few complications

The cases were divided into three groups for the evaluation of sulphapyridine therapy Those not responding to therapy even though the sputum was packed with pneumococci numbered seven and the lack of response was found to be due to unsuspected fluid, partial atelectasis of the lung or underlying tuberculous disease. There was no evidence that sulphapyridine therapy delayed lung resolution.

One case with purulent pericarditis who recovered, and interesting cases of staphylococcal and *B pyocyaneus* pneumonia are described.

The relation of the sulphapyridine induced, to the natural crisis is discussed.

I should like to express my thanks to Major B BLEWITT R.A.M.C for carrying out the laboratory investigations.

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KALA-AZAR IN EAST AFRICA

BY

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CONTENTS

In a previous article (Cole *et al* 1942) a description was given of an outbreak of kala azar in a battalion of King's African Rifles Since then other cases have been admitted to this military hospital, and it is possible not only to amplify the description of the course of the disease but to give and discuss the results of treatment, and to describe the late cutaneous manifestations

I General

A. Numbers of cases years of admission and results

In all sixty cases have been admitted of whom nine were not proved by finding the parasite, but in whom the clinical picture corresponded exactly

My thanks are due to the Director of Medical Services East Africa Command for permission to publish this article, and to Colonel Williams o.b.e. the O C Hospital.

They may for convenience be divided into three groups.

	Recovered.		Died.	Total.
	Proved.	Unproved.	Proved.	
1. 1941 cases from 2/3 KAR (described in previous article)	9	5	15	29
2. 1941 other cases	4	–	4	8
3. 1942 all cases	13	2	8	23

B. Place of Infection

Kala-azar has not generally been recognized or described as occurring in British East Africa, though Manson Bahr (1940) mentions northern Kenya vaguely. Kirk (1939), in a summary of the history and epidemiology of the disease in the Anglo-Egyptian Sudan, mentions particularly the western Abyssinian border and an area, Kapoeta, where the boundaries of Kenya, Abyssinia, and Uganda meet.

Of the groups of cases, those from the 2/3 KAR in 1941 were infected in the area north and west of Lake Rudolph in the neighbourhood of the Omo River. This area is near to Kapoeta, and contains sandflies in large numbers. Maximal infectivity seemed to be near the rivers, where there is moisture even in the dry season.

The other two groups, however, had no cases coming from this area. Some had been into southern Abyssinia as far as Mega, or even on to Addis Ababa, while others had never been north of Marsabit on the road which leads from Nairobi, via Nanyuki, Isiolo, Marsabit to Addis Ababa. Fifteen of the 1942 cases were from a Mule Transport Unit which had walked down this road from Addis Ababa to Nanyuki, taking 3 months on the journey. It seems, therefore, probable that there may be an endemic focus somewhere near this road south of Marsabit. This theory is confirmed by Heisch (1942), who found fever and splenomegaly amongst the Boran tribe, and in some cases was able to demonstrate leishmania. He was able to trace most of these cases to possible sources of infection on the Uaso-Nyero river which crosses the Isiolo Marsabit road at Archers Post.

C. Incubation Period

In the 2/3 KAR Group the incubation period could be assessed with reasonable accuracy, opportunity of infection commencing 10th February and the first symptoms during June, an interval of 4 months.

A group of cases in one Company started symptoms in the second half of July and August. This Company was particularly exposed to infection in the latter half of May, giving an incubation period of rather over 2 months.

This is comparable with the finding of KIRK (1939) in the Sudan, who suggested 3 to 6 months

An incubation period of 2 to 4 months was consistent with all the histories and in particular with the Mule Transport Unit This Unit was on the road from 12.2.42 until 12.5 42 and in the suspected region in the second half of April Cases began to present symptoms in July and August, an interval of 2 to 4 months

D PERIODICITY

It is noteworthy that both in 1941 and 1942, admissions occurred in the 4 months June to September Later cases were of long standing and had not been correctly diagnosed previously

The possible time of infection derived either by known travel in suspected areas or by deducting the suggested period of incubation must therefore have been March to June. This corresponds roughly with the rainy season in Northern Kenya, and is consistent with KIRK's conclusion that his maximal infectivity was from July to October the rainy season further north.

II SYMPTOMATOLOGY AND CLINICAL FEATURES.

A. ONSET

This may be sudden with headache and high fever or may be gradual with increasing fever and malaise, perhaps not reaching a maximum until the second week.

Twenty cases complained primarily of abdominal pain, seven of them with vomiting The pain was sometimes over the spleen or liver sometimes diffusely over the upper abdomen. Five cases presented as dysentery or diarrhoea, and six others were found to have loose stools with pus or blood cells Fourteen cases complained of pain in the chest or cough, or both two of these had a frank bronchopneumonia while the others had such physical signs as rhonchi or moist rales at one base Three complained of pain in the neck two with stiffness amounting to neck rigidity Five complained of sore throat due to moderate pharyngitis.

Cases admitted late in the disease might present as debility and anaemia.

The majority with or without other symptoms, gave a story of fever and malaise either sudden or gradual in onset.

B TEMPERATURE AND PULSE.

The only consistent feature of the fever is its irregularity and the height reached at some stage of the illness 104° to 105 F was generally attained Gradual rises and sudden onsets both occurred. A continuous high plateau-like course may change to a swinging remittent one Even without therapy there is an undulant tendency dropping 1 week to 99° to 100 F and then the next week rising to 103° to 104 F complete apyrexia for more than

24 hours was not noticed to occur spontaneously Two or more peaks of fever in the 24 hours were frequently observed.

There is a tendency for the pulse to be faster than it should be relative to the fever especially if the fever is not severe. This is perhaps due to the cardiac that occurs.

C CLINICAL APPEARANCE.

The majority of cases have been characterized by a remarkable appearance of fitness in spite of the fever Thus, a man with a temperature of 103° F might be seen walking around the ward and making a pretty fair effort at eating his bulky food ration. On questioning he would reply as often as not, that he had no complaint of any sort beyond a certain diminution of his customary vigour or he might complain of a slight headache or abdominal discomfort.

Examination would show a clean tongue, and few physical signs beyond fever and pallor of the mucous membranes Splenomegaly and enlarged lymph glands might also be noticed. In cases of long duration there might be severe wasting and oedema of the feet was seen even without severe anaemia.

In sharp distinction from the above, four cases were admitted in a typhoidal state, with dirty tongue and an apathetic manner Also in those whose condi tion deteriorated, symptoms of general weakness and toxaemia would develop

In fact while a moderate infection might be tolerated well, a more severe or overwhelming one would naturally produce a seriously ill patient.

Other clinical features are rigors, sweats, joint pains, and later some emaciation.

D SPLENOMEGALY AND HEPATOMEGALY

Extreme enlargement of the spleen is emphasized in all descriptions. It is not invariable and more important, it is a relatively late sign. Few of these cases were admitted absolutely at the beginning of the disease and yet eleven out of the sixty did not have palpable spleens while a further twelve had spleens enlarged only 1 finger s breadth. The average enlargement of the spleen on admission was 2 1 fingers breadth. This is a degree of enlargement that might be caused by malaria in a population not completely immune.

That splenic enlargement does almost invariably occur later in the disease is shown by noting the size reached during their hospitalization. Within 6 weeks only two cases did not develop a palpable spleen while the average maximum enlargement was 3·9 fingers breadth.

Splenic enlargement may vary rapidly and considerably One man thought to be cured, had a spleen only palpable on deep inspiration 2 days later in a relapse, it had expanded beyond his umbilicus. Others, on successful therapy might show a reduction from six or seven fingers breadth to nothing this reduction might be rapid—two to three fingers breadth in 4 days.

Reduction in the size of the spleen may be regarded as one of the criteria of cure. Of thirty-eight patients surviving twenty four did not have their

spleens palpable at all eight were only palpable on inspiration, and four were only one finger's breadth enlarged One was 2F + and one 3F + This contrasts with the findings of KIRK and SATI (1940a, b c and d) where 30 per cent. remained more than 2F +

Hepatic enlargement follows the same lines as splenic enlargement, but is slower in development and recession, is less marked, and occurs less often Of the sixty cases, forty-four had no hepatic enlargement on admission, but sixteen of these later developed some enlargement.

It must therefore be noted that while splenomegaly hepatomegaly or both, will nearly always develop sooner or later their absence in an early case does not exclude the diagnosis of kala azar

E. LYMPHATIC GLANDS.

Glandular enlargement occurred in exactly half *i e* thirty out of sixty cases (twenty-six of these were punctured for diagnosis) All groups of glands might be affected—cervical, axillary, epitrochlear or inguinofemoral but the latter were most marked. Enlargement was not great and the affected glands were firm and rubbery One case was admitted as lymphadenitis The finding of leishmania in a number of these glands indicates that enlargement is directly due to invasion by the parasites

F KIDNEYS

Damage to the kidneys, possibly as a result of the continued fever is of frequent occurrence. In forty cases where the urine was examined thirty-one showed albumin as a fair cloud or more, and in nineteen of these granular casts were also present In certain cases, not immediately diagnosed and treated albuminuria and nephritis developed as the disease progressed In fatal cases the kidneys were swollen under the capsule, and there was damage ranging from cloudy swelling to actual necrosis and degeneration of the renal tubules. This damage appears to be an indirect toxic effect, and not due to direct parasitic invasion.

G COMPLICATIONS.

1 *Haemorrhage* —There appears to be an increased tendency to bleed from mucous surfaces, though skin petechiae were only once seen and sub conjunctival haemorrhage once. This haemorrhagic tendency is particularly associated with a severe infection, often as a terminal phenomenon Epistaxis occurred in nine cases, all severe, and twice terminally Haemorrhage into or from the gums was seen in six cases Haematemesis and urethral haemorrhage were seen once each In seven cases severe bowel haemorrhage occurred terminally

2. *Diarrhoea.*—Five cases complained of dysenteric symptoms on entry and others were found to have pus or blood in the stools. Diarrhoea occurred at some stage or another in most patients illnesses and recurred frequently in those cases not doing well

The reason for the diarrhoea and the bowel haemorrhages can be realized from postmortem examinations when the large bowel was often found severely ulcerated.

3 *Bronchitis and pneumonia.*—The frequency of bronchitis or pain in the chest as a presenting symptom has already been mentioned. Many other cases developed minor degrees of bronchitis during their illness Two developed a definite pneumonia and recovered, in one a granulocytopenia was corrected by the infection. In three cases pneumonia was terminal.

4 *Pharyngitis sore throat dysphagia and cough with the expectoration of mucopus* in twenty cases at some time during their illness. The throat appearances were indefinite the pharynx appearing granular dry or gelatinous. The condition may be associated with granulocytopenia. It seemed to be much less common in 1942 than in 1941 possibly because more effective treatment reduced the period of granulocytopenia.

5 *Anaemia*—Secondary anaemia developed in all cases and in some was so marked as to be the most important symptom it was in part due to haematopoietic depression, but in part to loss in epistaxis dysentery etc. It could develop rapidly *e g* a drop of from 50 to 20 per cent. Hb in less than two weeks, and took a long time to recover

Severe anaemia, less than 30 per cent. Hb occurred in nine cases. Transfusion would, of course, correct the anaemia, but the need for 2,300 c.c. to raise one case from 12 to 32 per cent. Hb shows that blood loss and destruction can be rapid.

6 *Oedema*—This occurred in ten cases—usually in the feet, but three times as a general anasarca. It was connected with the anaemia, but not absolutely for some cases with severe anaemia did not develop oedema, whereas other cases with moderate haemoglobin did thus, two cases with 15 per cent. or less haemoglobin had no oedema, and cases with 64 and 50 per cent. showed it.

It seems probable that oedema is connected with the shift of plasma proteins from albumin to globulin, which is known to occur in this disease, and of which shift the formol-gel test is an expression. No estimations, however of plasma proteins were performed All cases with oedema had albuminuria and granular casts.

Oedema was relieved by blood transfusion, and once by plasma transfusion. It is essentially a late complication either after a long illness or where seriously ill.

7 *Dental Infections*—It has been suggested that in kala-azar or perhaps in the treatment by 4 4 -diamidino stilbene, there is a tendency to pyorrhoea and dental abscess. I do not think that the records confirm this out of sixty cases, four needed extraction of teeth for root abscess, while one developed a necrosis of his palate and severe pyorrhoea. Only two of these five were on treatment with 4 4 -diamidino stilbene. I do not think this is a higher incidence

than would occur naturally with patients making a prolonged stay in hospital, though of course the granulocytopenia present might predispose to dental infection.

There is however a symptom which has occurred in 60 per cent. of cases and actually led to the diagnosis of cases elsewhere This is pain in the teeth and gums without any obvious dental abnormality Its causation is not known.

H DIFFERENTIAL DIAGNOSIS

This can only indicate those diseases which most clearly simulated kala azar or which gave most trouble, in this particular area

Perhaps the most graphic method would be to give the various diagnoses on the Field Medical Cards or Sick Sheets with which the patients were admitted —

Malaria	24	Pulmonary T B	1
Bronchitis	6	Encephalitis	1
Influenza	3	Lymphadenitis	1
Dysentery	3	No diagnosis (including P U O N Y D Fever Splenomegaly etc.)	17
Tonsillitis	2		
Typhoid	2		

This demonstrates what was an obvious feature that the illness was confused with *malaria*. To complicate things further seven out of the twenty-four above had positive blood slides and practically all cases were given quinine In fact, as a general rule, absence of response to anti-malarial therapy is one of the steps in diagnosis

The continued fever even after other signs had disappeared demonstrated that we were not dealing with straightforward cases of *bronchitis influenza, dysentery* or *tonsillitis* This would be confirmed by low polymorph counts, or splenomegaly or both.

Typhoid was excluded by the results of culture and Widal tests *Pulmonary tuberculosis* presents more difficulties than might appear for the miliary type produces a fever just like kala azar and definite leucopenia and may not show characteristic X ray appearances while positive sputa are seldom found

Amoebic hepatitis was also a difficulty but the higher polymorph count should differentiate it speedily

Visceral syphilis with enlargement of spleen and liver may resemble kala azar The responses to anti syphilitic treatment and the absence of prolonged pyrexia differentiate

Finally probably the closest resemblance is borne by *undulant fever* Sporadic cases of this disease occur in the same area. It produces a long continued often irregular fever and a definite leucopenia and splenic enlargement while other incidental complications are similar to those of kala azar Of course agglutination tests or cultural isolation if available should serve to differentiate If not the following clinical points may be of help greater frequency of joint

pains, spleen seldom greater than 2F + patient feels more sorry for himself, and leucopenia and anaemia seldom so marked.

5 SKIN RASHES.

MANSON BAHR (1940) mentions a condition recognised by BRAHMACHARI in India and described under the name of dermal leishmanoid or post-kala azar leishmaniasis. This is a sequel to treated cases of kala azar occurring about 1 year after the disease. There is, according to him, first a stage of depigmented spots, followed by a stage of papules varying in size from a pin's head to ½ inch diameter. The condition may apparently last several years and ulceration may occur. Leishmania may be found in smears from the lesions.

KIRK *et al* (1938 and 1940) describe a similar condition which they differentiate from oriental sore and espundia. This is a fine punctate papular rash occurring in cases of visceral kala azar during or just after treatment. In the first article they state that leishmania are not present in the rash and speculate whether it is due to the kala azar or to the antimony treatment. In the second they give a fuller description: the rash is first finely punctate, but later may become coarser and frankly papular; ulceration does not occur; the rash occurs during treatment after about 15 injections of stibosan and has occurred after treatment with diamidino stilbene, a non-antimonial drug; the rash commences on the face and may be confined to this area, or may spread over the trunk, and rarely on the limbs; there is no itching; contrary to Indian experience it tends to disappear spontaneously within a few months; in about 12 per cent. of cases leishmania have been demonstrated in scrapings from the papules.

KIRK *et al* speculate as to whether the rash is an allergic phenomenon, why it occurs only when the visceral lesions abate, and whether it has any prognostic significance.

Incidence.—Out of 60 cases of the series, no less than eighteen developed a definite cutaneous rash, a proportion of 30 per cent. More remarkable still is the relation of the rash to recovery: out of twenty two fatal cases only one developed the rash, this a man who lived for 140 days and had had a full course of tartar emetic with some remission in his illness before he eventually succumbed; with thirty-eight cases who recovered, seventeen developed a rash *i.e.*, 45 per cent.

Drugs.—All the rashes developed after one or more courses of therapy and at a period when there was a remission in or cure of the disease. Drugs used before the rashes developed were:—

	Cases.		Cases.
Urea stibamine	6	Diamidino stilbene	3
Tartar emetic	4	Anthiomaline	1
Urea stibamine and diamidino stilbene	4		

Onset —The rash always commenced on the face and in four cases it did not spread further In the rest it spread on to the neck and upper trunk. In five cases it spread on to the limbs and lower trunk later It was always most extensive and developed on the face.

In five cases the onset of the rash was associated with fever sweating and constitutional disturbance in a patient previously apyrexial. Twice this procedure was duplicated a second disturbance heralding the appearance of the rash on the body

Description —The rash always commenced as a fine miliary eruption rather like a perifollicular or sudaminal hyperkeratosis. This may last for a little and then fade, or it may progress into larger papules usually fewer in number These are acneiform and hyperkeratotic at first, but then extend and flatten into plaques exactly like a lichen In two extreme cases warty growths formed on the nose and cheeks Ulceration does not occur Itching did not occur unless there was secondary infection.

Retrogression —Fading of the rash occurred in the reverse order to its appearance. Miliary punctae would disappear ,while the larger papules would flatten, dry and atrophy The extreme warty growths actually fell off leaving more or less normal skin beneath. Disappearance of the rash occurred in all cases before leaving hospital, in a period of from 1 to 4 months

Parasites —In twelve of the eighteen rashes a scraping was examined microscopically and in eight or 66 per cent of these leishmania were demonstrated In two cases this was actually the way a previous clinical diagnosis was confirmed, spleen and gland punctures having failed to reveal the parasites. In three cases where multiple face scrapings were carried out, no leishmania could be demonstrated in the earliest very fine eruption but were found later when the rash grew more obvious. Parasites were generally very frequent in a fully developed rash, and there was little difficulty in demonstrating them In all cases, the parasites disappeared from the rash and the skin before the rash itself finally went, and in no case on leaving hospital could they be demonstrated

I think therefore, that sufficiently frequent and careful examinations would demonstrate leishmania present at some stage in the rash, and that they do not occur in the skin otherwise

Conclusions

There appears to be no doubt that the rash is associated with leishmania infection rather than with a drug It occurs only when the patient is improving after therapy in these cases, but possibly also during natural recovery

I think from these data a reasonable theory may be constructed. The leishmanial infection is evidently being overcome in the internal organs by the combination of drug and bodily resistance A process then occurs somewhat analogous to the spore formation in bacteria or protozoa when conditions

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C CAUSE OF DEATH

While of course kala azar was the primary cause many cases died of complications of various kinds, and it is these causes or modes of death that I propose to analyze —

Dysenteric	5	Typhoidal	4
Myocardial failure	5	Asthenia	3
Pericarditis	2	Anaemia	1
Pneumonia	2		

1 *Dysentery* —Three of these had severe haemorrhage terminally and this also occurred terminally in four of the other cases The dysentery was persistent and refused to react to any form of treatment. Leishmania were not seen in the stools examined

Dysenteric symptoms beforehand occurred in cases with other modes of death Severe ulceration of the large, but not the small bowel was found post mortem to account for the symptoms

2. *Myocardial Failure* —There was a characteristic appearance post mortem of a flabby heart with a gelatinous degeneration In two cases, death occurred within 2 hours of an injection of tartar emetic, and it is probable that this drug may have contributed to some of the other deaths.

3 The cases of *pericarditis* were pneumococcal and the distinctive and fatal part of a commencing septicaemia

4 Only two cases dying of *pneumonia* may give perhaps a wrong impression for in seven other cases some degree of bronchopneumonia was found postmortem

5 The *typhoidal type* of death, while of course just a product of severe toxaemia was quite a definite entity in the 1941 cases. The patients were severely ill with high fever and dirty tongues, they gradually deteriorated and became semi-comatose Before death there was often diarrhoea and epistaxis

6 The *asthenic type* did not present the same signs of toxaemia. They merely became weaker and weaker and might develop oedema or pneumonia as well as diarrhoea and epistaxis before fading out.

7 One case appeared to die of *rapidly increasing anaemia* due in part to blood loss from epistaxis and bowel haemorrhage He died before transfusion could be arranged.

D POSTMORTEM FINDINGS

Heart —Oedematous and flabby with a sort of gelatinous appearance in every case

Lungs —No specific change though often a terminal pneumonia

Liver —Some enlargement and congestion was the rule In two cases fatty degeneration of the nutmeg type was seen and in two a fine portal cirrhosis. Leishmania often present

Spleen —Enlargement invariable, often very marked. Firm splenic tissue, but not excessively hard and fibrous. Leishmania often present.

Kidneys —All cases showed cloudy swelling of the kidney and oedema of the perinephric tissue In three cases there was necrosis and partial disintegration of the lining of the convoluted tubules.

Bowel.—Inflammation and mucosal damage was frequent Marked ulceration of the large bowel was noted in four cases, and oedema of the bowel wall in two others.

Glands —In addition to the tendency already mentioned to lymphadenitis of external lymph glands, the mesenteric lymph glands were noted to be enlarged in four cases

Bone Marrow —There was a tendency to hyperplasia. In two cases red marrow was noted in the tibiae Leishmania always present.

General – Emaciation anaemia and oedema of the tissues were frequently seen

IV Haematology and Laboratory Diagnosis

A Red blood cells and haemoglobin

A secondary anaemia develops sooner or later in all cases. As mentioned under complications, this may be so severe as to be the most important symptom. It is probably due to a combination of causes, epistaxis and bowel or other haemorrhage on the one hand, and a depression of the haemopoietic function of the marrow by toxaemia and also direct parasitic invasion on the other

The average of blood counts on admission for all cases was 56 per cent haemoglobin and 3,365 000 R B C per c.mm. the range being from 90 per cent. haemoglobin and 5,200 000 R B C to 17 per cent. haemoglobin and 1,300,000 R B C

If these cases were not diagnosed and treated at once, the anaemia could become rapidly more severe Examples are 80 per cent. Hb and 4,380 000 R.B C on entry down to 30 per cent. Hb and 2,120 000 R.B C after 5 weeks 90 per cent. Hb and 4 760 000 R.B C on entry down to 30 per cent. Hb and 2,180 000 R.B C after 6 weeks and 50 per cent. to 20 per cent Hb in 2 weeks.

If we take the average of the lowest blood counts recorded for each patient we get the much lower figure of 37 per cent. haemoglobin and 2,520 000 R.B C. a figure which would have been lower still if more blood counts had been done at the worst stages

The anaemia does not react satisfactorily until the disease has been completely eradicated. Even then the response to adequate doses of iron, good diet, and a fair amount of liver by mouth, was very slow several weeks or months being needed for more or less normal levels to be reached This is similar to the anaemia of chronic malaria.

The average of blood counts on discharge was 72 per cent. haemoglobin and 4 165 000 R.B C per c mm which though low is not far below the average

African count. Patients were not discharged until they had been at least 2 months well and symptomless.

Blood slides showed no gross abnormalities; there was some poikilocytosis and anisocytosis; the appearance probably approximates to that of TROWELL'S (1942) dimorphic anaemia.

Marrow smears were examined, more from the diagnostic than the haematological point of view; and in any case require considerable experience to interpret; but no marked changes were noted except in long standing cases where the macrocytic cells containing leishmania presented a special and remarkable appearance.

B. WHITE BLOOD CELLS AND DIFFERENTIAL COUNT

The alteration in the white blood cells is very characteristic of the disease and is of value in diagnosis. The alteration is two fold: a severe leucopenia, and an even more severe granulocytopenia with a shift in the differential count to the lymphocyte. This change appeared to occur early in the disease, without any recovery until symptoms had ceased for a long while.

The white count improves as a result of the treatment but only very slowly and even on discharge, after 2 to 3 months without fever or any signs of infection, still remain low. This, however, may not be due to kala azar as there is a tendency in all white counts in Africans for the normal excess of granulocytes over lymphocytes and mononuclears to be lost.

Average counts of 57 cases on entry.

Total W.B.C. 3,100 (Polymorphs 1,300 = 41 per cent.)

Varying from W.B.C. 2,200 (P. 220 = 10 per cent.) and W.B.C. 1,000 (P. 600 = 60 per cent.) to W.B.C. 6,600 (P. 2,000 = 30 per cent.) and W.B.C. 5,200 (P. 2,700, 53 per cent.)

Average counts of 37 cases on discharge.

Total W.B.C. 4,500 (Polymorphs 2,250 = 50 per cent.)

Varying from W.B.C. 2,400 (P. 1,000 = 38 per cent.) to W.B.C. 7,400 (P. 5,600 = 74 per cent.)

In fact, the numbers of polymorphs on discharge were nearly double the numbers on admission.

In two cases agranulocytosis occurred. One of these died; the other was stimulated to granulocyte production by an attack of lobar pneumonia. Granulocyte production can also be stimulated by other diseases, *e.g.* a rise from W.B.C. 1,400 (450 polymorphs) to 16,000 (12,000 polymorphs) after an attack of dysentery.

C. FINDING OF LEISHMANIA

This has meant in practice the examination of smears from living tissues and smears and sections from postmortem material.

The following tissues were examined:—

Spleen: smears from puncture, and postmortem [illegible]

Lymph glands smears from puncture, and after biopsy
Bone marrow smears from puncture, and postmortem material.
Liver smears from puncture, and postmortem material.
Skin scrapings from dermal lesions.
Tonsillar and nasal swabs.
Dysenteric material.

Culture of the leishmania from the blood and from splenic material has also been tried.

Results of puncture and the examination of postmortem material —

	Puncture			Postmortem.		
	Total.	Positive.	Per cent.	Total.	Positive.	Per cent.
Spleen	41	25	60	15	14	93
Liver	11	3	27	13	7	54
Bone marrow	9	1	11	1	12	100
Glands	7	1	14	6	5	83

Spleen Puncture —This was performed for diagnosis on forty-one occasions and on twenty five of these leishmania were found. These were usually very scanty and found only after prolonged search in early cases, though in cases not diagnosed till after several weeks or months a large number of parasites might be found No accidents or complications from puncture occurred. The route between the ribs was preferred to the subcostal, as the spleen could be fixed better with less risk of tearing and as it is easier to hit a relatively small spleen by this method. A moderately large bore needle was used with an all-glass syringe to apply suction. It is essential that the needle and syringe be dry sterilized to avoid distortion of the parasite.

Postmortem Out of fifteen cases where spleen material was examined postmortem, in only one were the leishmania not detected. They were, however often very scanty

Liver —Puncture performed on eleven occasions, only three of which gave a positive result for leishmania.

Postmortem Out of thirteen cases examined, seven were positive and six negative Although one case was diagnosed by liver puncture after a negative spleen puncture there do not appear to be as many parasites in this organ.

Bone Marrow (sternal puncture).— Only one positive in nine examinations

Postmortem Twelve examinations, all positive.

The poor results of sternal puncture were due to the infrequent use of this method and then on cases where parasites were difficult to detect. The results of examination of postmortem material show that the parasites are probably as frequently present as in the spleen.

Glands—Puncture was performed in twenty seven cases, in twelve of these the parasites were found

Postmortem Only six cases were examined and five of these were positive

Skin Rashes—Twelve examined and in eight of these the parasites were found

Tonsillar and Nasal Swabs—Smears from six cases were examined. All were negative

Dysenteric Material—Two attempts to find leishmania were unsuccessful

Blood Culture—Attempted in ten cases using N N N medium or citrated blood. All results negative

Spleen Culture—Two attempts were made on material from postmortem One was successful, flagellate forms were seen on the 17th day and increased in number for 14 days till the culture became contaminated

Summary

The parasites are scanty early in the disease but may become almost incredibly numerous later They are both intra and extra-cellular They are not invariably commonest in any one organ, and a negative result from one should be followed by examination of others

From the point of view of convenience and lack of trauma to the patient it is wisest to start with a gland puncture, and if this is negative to perform spleen or sternal punctures

Liver puncture is probably only of value where this organ is grossly enlarged.

Skin scrapings should always be examined when a rash is present Other tissues and methods seldom give positive results

D OTHER LABORATORY TESTS

The formol gel reaction is negative in early cases (no result in twenty-one tried) It does, however become positive in late cases who have had pyrexia for 3 or 4 months

No other tests were tried.

V TREATMENT

A. DRUGS USED

In 1941 tartar emetic (sodium antimonyl tartrate) intravenously was the only drug of any value tried though some cases were given tryparsamide without particular effect. Anthiomaline (an organic trivalent antimonial) was not tried seriously until 1942 when it was used intramuscularly in two cases without accessible veins one a fresh case and the other a relapse

Two other drugs became available in 1942 urea stibamine (BRAHMACHARI), an organic pentavalent antimonial and M & B 744 or 4 4 diamidino stilbene

(WARRINGTON YORKE) a drug not containing antimony both of these for intravenous use.

B CASES NOT RECEIVING ANY OF THESE FOUR DRUGS

Nine cases (seven died, all proved two lived, one proved).

1 Treated quinine, sulphapyridine, blood transfusion, died after 38 days. Proved P.M.

2. Treated quinine, and anti-dysenteric measures. Died after 15 days. Proved P.M.

3 Treated M.A.B 5 0·6 gramme. Tryparsamide 2 × 1·5 grammes. Died after 54 days. Proved P.M.

4 Treated quinine, sulphapyridine. Died after 47 days. Proved P.M.

5 Treated tryparsamide 12 grammes. Spleen puncture positive. Died after 24 days.

6 Treated tryparsamide 12 grammes (optic neuritis) Spleen puncture positive. Died after 75 days.

7 Treated quinine Spleen puncture positive Died after 24 days.

8 Treated tryparsamide 11 grammes with no result. Fever subsided spontaneously later 160 days fever 66 days observation. Not proved.

9 Treated tryparsamide 16 grammes with no result. Fever subsided later after mumps. Sternal puncture positive 45 days fever 45 days convalescent observation.

There was little or nothing to suggest that tryparsamide exerted any effect on the course of the disease.

C. TARTAR EMETIC.

These are probably best divided into those receiving only partial courses (less than 15 grains) those receiving full (25 grains) or even multiple courses, and those receiving first tartar emetic and later other drugs.

Tartar emetic was administered intravenously as for bilharziasis, in a strength of 1 grain in 2 c.c. water dosage 1 1½ 2, 2, 2, 2½ up to 25 grains injections alternate days.

Partial Courses

1 Gland puncture positive Tartar emetic 15 grains. No response. 96 days in hospital. Died 30 days after course.

2 Liver puncture positive T.E 14½ grains. No response Died during course. 33 days in hospital.

3 Postmortem positive T.E. 13 grains Temperature normal 2 weeks, but refused further treatment. Died 88 days after course 117 days in hospital.

4 Spleen puncture positive T.E. 7 grains Some response but died of dysentery during course. 45 days in hospital.

5 Spleen puncture positive. T.E 8½ grains. No response Collapsed and died after injection. 97 days in hospital.

6 Spleen puncture positive T.E. 9 grains. No response Died during treatment. 22 days in hospital

7 Not proved. Clinical diagnosis only T E. 14½ grains 12 weeks febrile before tartar emetic. 5 weeks afterwards no relapse

Full Courses

1 Postmortem positive T E 27½ grains. Temporary improvement half way through course later deteriorated. Died 26 days after course 62 days in hospital.

2 Postmortem positive T E 27½ grains No response Died 25 days after course 97 days in hospital.

3 Spleen puncture positive. T.E. 25½ grains Temperature down 5 days Died 60 days after course. 92 days in hospital.

4 Postmortem positive T E 24 grains No response Died 72 days after course. 140 days in hospital.

5 Liver puncture positive T E 28 grains Temperature down 7 days Died 48 days after course 89 days in hospital.

6 Postmortem positive T E. 25½ grains Temperature down 7 days Died 90 days after course 131 days in hospital.

7 Spleen puncture positive Two courses T E. 20 and 21 grains Temperature down during first course but spleen did not shrink from 4F + to 1F + until second course Afebrile 7 months and spleen less than 1F + 2 months before discharge

8 Spleen puncture positive T E 25 grains Afebrile after five injections Spleen shrank from 4F + to nil. 9½ months observation without relapse

9 Spleen puncture positive T E. 22 grains Good response afebrile spleen shrank from 2F + to nil. 1½ months observation without relapse

10 Not proved clinical diagnosis T.E 39½ grains (two courses) Afebrile during second course 5 weeks observation without relapse

11 Not proved, clinical diagnosis T.E 26 grains Temperature down half way through course. 1½ months observation without relapse.

12 Not proved clinical diagnosis. T.E 25 grains Temperature dropped towards end of course 2 months observation without relapse

Cases that Relapsed and were later Treated with Other Drugs

1 Liver puncture positive T.E 21½ grains Temperature down half way through course and afebrile 1 month then relapsed. T E 30 grains Temperature dropped after three injections Relapse after 3 weeks T.E 20 grains Temperature dropped towards end of course Relapse after 3 weeks At no point did the spleen shrink, but rather increased.

2 Skin rash positive (later) T.E 25 grains Temperature down after five injections but rose immediately they ceased. Spleen increased.

3 Spleen puncture positive T E. 28½ grains Afebrile 3 weeks before relapse spleen remained large

4 Spleen puncture positive T.E. 25½ grains No complete remission. Spleen remained large

5 Spleen puncture positive T E. 32 grains Remission 2 weeks then relapse.

6 Spleen puncture positive T.E. 24½ grains Remission half way through. Relapse after 4 weeks Another remission lasting 5 weeks after pneumonia.

7 Gland puncture positive T.E. 35½ grains. No response.

8 Spleen puncture positive T E 12½ grains Afebrile for 1 month. Slight fever for a week and then afebrile for 5 weeks before relapse. Spleen remained large

Summary and Conclusions regarding Cases treated with Tartar Emetic

Out of twenty-seven cases treated with tartar emetic, twelve died and seven recovered without other treatment, but of these latter only three had the diagnosis confirmed by discovery of the parasites. In addition, remissions

varying from 5 days to 5 weeks were produced in eleven cases, and no appreciable remission in nine cases. This gives a recovery rate of 25 per cent. (all cases) or 11 per cent. (microscopically proved) under tartar emetic treatment which is not much better than the figures for "No treatment at all," viz., 22½ per cent. (all cases) and 11 per cent. (microscopically proved).

However some of the cases, afterwards cured by other drugs, were presumably kept alive by the tartar emetic until other drugs became available, and this value of tartar emetic is confirmed by the 55 per cent. of temporary remissions produced by its use in non-successful cases.

Tartar emetic is not a pleasant drug: it produces cough, chest pain, and great depression, just after injection, so that patients have often refused to continue with it: it is easy to damage the veins with it and to produce abscesses in the arm: and it is a definite poison with an action on the heart, for one case died of sudden heart failure within an hour of injection, and others appeared to be hastened towards heart failure by it. Pathological changes in the electrocardiograph during the treatment have been discussed by MAINZER and KRAUSE (1940).

Tartar emetic appears to be valuable in the treatment of kala azar in India and Assam (MANSON BAHR, 1940) but not in China or the Sudan (KIRK and SAFI, 1940). Experience in this series resembles the Sudan cases. Tartar emetic should never be used if other drugs are available, but in their absence it is perhaps better than nothing.

D. ANTHIOMALINE.

(A trivalent lithium salt of antimony.
2 c.c. ampoule contains 0·01 gramme antimony.)

This drug was used in a half hearted way in 1941, giving one or two injections intramuscularly with no obvious results. Two cases were successfully treated by it in 1942.

1. Leishmania found in excised gland. No accessible veins. Treated by injections of 4 c.c. anthiomaline intramuscularly on alternate days until 78 c.c. were given. Temperature down by slow lysis between fifth and tenth injections, *i.e.*, after 40 c.c. Developed cutaneous leishmanoid rash. No relapse after 7 months. No untoward results of injections.

2. Spleen puncture positive. Had courses of tartar emetic (30 grains), diamidino stilbene (1·15 grammes, 1·01 grammes, 1·13 grammes), and urea stibamine (2·15 grammes) with relapses after each. Spleen had increased to 5F + but shrank after urea stibamine to 3F +. Was running fever 99 to 101° F. for a fortnight when anthiomaline commenced, as all veins had by now been destroyed. 4 c.c. was given intramuscularly on alternate days to 56 c.c. Temperature normal by fifth injection. Treatment ceased on account of gluteal abscess from injections. No relapse after 6 months (previous longest intermission 7 weeks). Spleen only palpable on respiration.

These two cases suggest that anthiomaline is a useful adjunct where intravenous therapy is difficult or impossible. Large and intensive dosage is necessary, such as 60 to 80 c.c. given 4 c.c. at a time on alternate days.

E. UREA STIBAMINE

A compound of urea with p-aminophenylstibinic acid, introduced by (and apparently manufactured by) BRAHMACHARI He suggests two methods of dosage for adults Standard 0·05 gramme, rising to 0 15 or 0 2 gramme intravenously in distilled water, giving injections twice a week until symptoms disappear Intensive Daily injection 0·05 rising to 0 15 gramme for 7 to 10 days, total dosage 1 5 grammes

This drug has proved to be the most valuable we have hitherto tried, but our dosage has differed from that of BRAHMACHARI We have used it according to three different schemes —

(*a*) *Slow dosage*

(corresponding roughly with BRAHMACHARI s standard dosage)

Injections every 2 to 3 days, starting 0·05 gramme and gradually rising Total 2 0 to 2 5 grammes in 15 to 25 injections in 20 to 50 days

Eleven cases were treated by this method (all confirmed microscopically) The average time for the temperature to come down to normal was 20 days and varied between 13 and 35 days Five cases relapsed later

Reactions Two cases showed a rise in temperature with the first two injections, presumably due to parasite destruction a few complained of tightness in the chest after injection

Evidently this dosage, while it eventually brings down the temperature is not adequate, as nearly 50 per cent of relapses occurred This is confirmed by one case who did not even respond to the spaced injections but responded without relapse when injections were given daily

(*b*) *Recommended Course*

(corresponding roughly to BRAHMACHARI s intensive course but more drug given)

The patient is given 14 daily injections of 0·05, 0 1, 0 15, 0 2, 0·2, etc Total 2 5 grammes

Nine patients were treated by this method (seven confirmed microscopically) The average time for the temperature to come down to normal was 5 days and varied between 3 and 8 days No relapses occurred Four of these cases showed the reactionary rise of temperature after the first or second injection but no other ill-effects were noted.

This is the recommended treatment for all normal cases but may perhaps need modification for cases that have been missed for long periods (See next paragraph.)

(*c*) *Fatal Cases*

Three cases died when under treatment with urea stibamine All these had been ill for a considerable period with the disease before diagnosis and in

contrast to early cases had very large numbers of parasites present. All were anaemic, and in a low state. They died, with some exacerbation of symptoms, after the sixth or seventh injection (0·9 to 1·1 gramme).

It seems possible that where there are large numbers of parasites and great debility the patient's condition should be built up by transfusions until a level of 50 per cent haemoglobin is reached and that small doses (0·05 gramme) should be used for the first week. On the other hand, equally decayed or anaemic patients did well on the recommended course, and these patients might have died in any case.

(d) *Intensive Course*

Five cases who had relapsed after previous treatment with urea stibamine (slow dosage) diamidino stilbene, tartar emetic or multiple treatments were successfully cured with an intensive course. This idea was suggested by the improvement in results with the relatively intensive rather than slow course and the absence of unpleasant symptoms.

The dosage used was 0·1 0·2 and 0·3 gramme daily up to 2·7 grammes in ten injections. The temperature came down in 3 to 5 days and there were no relapses. Rapid shrinkage of the spleen also took place.

Summary of Cases treated with Urea Stibamine

1. Skin scraping positive (later). Relapses after temporary improvement with courses of tartar emetic (5 grains) and diamidino stilbene (970 mg.). Given 2·0 grammes of urea stibamine (rather slowly eighteen injections in 41 days). Temperature settled after 21 days, but spleen increased from 2F + to 3½F +. A papular rash developed on his face. He relapsed 1 week after completing the course temperature rising rapidly and severe epistaxis occurring. Then given diamidino stilbene (1·10 grammes, and 1·30 grammes and 1·31 grammes) in the course of the next 7 months with temporary improvements followed by relapses. Finally given an intensive course of urea stibamine (2·7 grammes in ten daily injections) temperature settled in 3 days, and spleen shrank to 5F + from being well beyond the umbilicus towards the R.I.F. This was followed, after a month's interval, by a second similar course, as the spleen was still 5F +, and he had slight fever again. Two months after this the spleen was not palpable, he had no further relapse and his dermal leishmanoid (which had been positive) had dried up and disappeared and was negative for leishmania. 4 months later well and fit.

2. Spleen puncture positive. Relapses after temporary improvements with courses of tartar emetic (grains 30), and diamidino stilbene (1·15 grammes 1·01 grammes and 1·13 grammes). Given 2·15 grammes urea stibamine in seventeen injections over 60 days. His fever did not come down until the end of the course and he relapsed after a fortnight. Later cured with anthiomaline.

3. Gland puncture positive. Relapses after temporary improvement with courses of tartar emetic (35½ grains), diamidino stilbene (960 mg.). Given urea stibamine 2·4 grammes in 20 injections over 48 days. Temperature did not come down until after 25 days. *One* month later no relapse spleen had shrunk from well below the umbilicus to 1F +. Two months later very well, no relapse.

4. Gland puncture positive. No response to diamidino stilbene (930 mg.). Given urea stibamine 2·05 grammes in twenty two injections over 53 days. Temperature came down half way through course. No relapse in 5 months.

5. Gland puncture positive. Given urea stibamine 2·5 grammes in 14 daily injections. Very severely ill with epistaxis, bilateral otitis media, anaemia (10 per cent. Hb)

needing 2½ litres of blood transfusion, and also bed sores Temperature down by end of course Spleen shrunk to nil from 3F + 3 weeks later developed dermal leishmanoid (positive scraping) with some fever Was given a second intensive course of urea stibamine (2 7 grammes in nine daily injections of 0 3 gramme) Fever may have been due to large abscess in thigh. No relapse after 6 months.

6 Spleen puncture positive. Given urea stibamine 2·65 grammes fourteen daily injections Temperature down after third injection. Spleen shrank from 1F + to nil. No relapse in 6½ months.

7 Spleen puncture positive. Diamidino stilbene 1 25 grammes relapse after 3 weeks Intensive urea stibamine (2 7 grammes sixteen daily injections) Afebrile after 5 days Spleen shrank from 2F + to nil. No relapse in 5½ months

8 Spleen puncture positive. Diamidino stilbene 1·05 grammes relapse after 3 weeks Urea stibamine 3·65 grammes spread over 42 days temperature down half way through course and spleen down from 4F + to just palpable. 3 weeks later dermal leishmanoid (positive scraping) 5 weeks later spleen increased gradually to 3F +, and a very slight evening pyrexia of less than 99 developed. Intensive urea stibamine (2 3 grammes eight daily injections) caused the spleen to shrink to nil and also the rash to dry up and become negative. No relapse in 4 months.

9 Gland puncture positive. Urea stibamine 2·05 grammes 18 daily injections Reactive high fever after two injections temperature down after ten. 1 week after completion of course (2 weeks afebrile) relapse. Given diamidino stilbene (1 21 grammes) response with febrile production of dermal leishmanoid, but relapse after a month. Intensive urea stibamine (2 7 grammes ten daily injections) brought temperature to normal after 4 days and spleen from 8F + to 1F + in less than 4 weeks No relapse in 6 months

10 Spleen puncture positive Urea stibamine 3·05 grammes 18 injections in 29 days (daily injection last 9 days) Temperature dropped when treatment was intensified. Spleen shrank from 2F + to nil. Developed dermal leishmanoid (positive scraping) 6 weeks after course which faded and became negative in 1 month. No relapse in 8 months.

11 Skin scraping (later) positive Urea stibamine 2 55 grammes in fourteen daily injections Reactive peaks of fever after first three injections temperature down to normal after six Dermal leishmanoid developed 2 to 3 weeks after course with positive skin scraping. Rash faded and became negative in 1 month. No relapse after 7½ months

12 Gland puncture positive. Remission and relapse with diamidino stilbene 1 25 grammes Urea stibamine 2 15 grammes 18 injections in 43 days Temperature normal after 20 days two febrile reactions later with appearance of dermal leishmanoid on face and then on body (skin scraping positive) Afebrile for 14 days then relapse Steady increase of spleen from 2F + to 8F + Intensive urea stibamine (2 7 grammes ten daily injections) temperature down in 4 days spleen to 1F + in 16 days In 2 months rash atrophied and negative No relapse in 6 months

13 Spleen puncture positive Urea stibamine 2·5 grammes in fourteen daily injections Reactive hyperpyrexia second injection afebrile after four Spleen 1F + disappeared by end of course Slight rash lasting 14 days developed 7 days after course No relapse in 8 months

14 Spleen puncture positive Urea stibamine 2·5 grammes in fourteen daily injections Reactive peak of fever after first injection Afebrile after 5 days Spleen 1F + to nil by end of course No relapse in 8½ months

15 Gland puncture positive Urea stibamine 2 5 grammes in 14 daily injections Reactive peak of fever after first injection Afebrile after 5 days Spleen 3F + to nil by end of course. No relapse in 8 months

16 Spleen puncture positive Urea stibamine 2·5 grammes in 14 daily injections Initial reaction afebrile after 3 days Spleen 6F + to 1F + by end of course No relapse after 8½ months

17 Gland puncture positive Urea stibamine 2 45 grammes in 10 daily injections Afebrile after 14 days Spleen 1F + to nil by end of course. Slight fever at end of course for 2 days with appearance of dermal leishmanoid which faded in 6 weeks No relapse after 8½ months

18. Spleen puncture positive. Urea stibamine 2·10 grammes in 17 injections in 26 days. Afebrile after 13 days. Spleen remained large, 3F + by end of course, but disappeared in the next 2 months. No relapse in 8 months.

19. Gland puncture positive. Urea stibamine 2·10 grammes in 15 injections in 31 days. Afebrile after 14 days. Spleen 3F + to nil. No relapse in 10 months.

20. Not proved microscopically. Urea stibamine 2·5 grammes in 14 daily injections. Afebrile after 5 days. Spleen 4F + to nil. No relapse in 6 months.

21. Not proved microscopically. Urea stibamine 2·6 grammes in twelve daily injections. Before treatment epistaxis, fever, anæmia 17 per cent. necessitating transfusion. Spleen 6F +. Temperature down in 8 days. Spleen 1F + at end of course 1 month later Hb 60 per cent. and spleen not palpable. No relapse in 6 months.

22. Postmortem positive. Died of dysentery after 1·10 grammes urea stibamine. Very large number of leishmania.

23. Gland puncture positive. 5 months undiagnosed. Anæmia and general oedema, Hb 40 per cent. two blood transfusions and 1·20 grammes urea stibamine. Died of pneumonia. Very large number of leishmania.

24. Spleen puncture positive. Urea stibamine 0·9 gramme: haemoglobin dropped quickly to 15 per cent. Died partly of anæmia before transfusion could be given. Large number of leishmania.

F. 4·4 DIAMIDINO STILBENE OR M. & B. 744.

This drug was introduced by Prof. Warrington Yorke (Lourie and Yorke, 1939) and found to be trypanocidal and also of value in Indian kala-azar (Adams and Yorke, 1939). Kirk and Sati (1940) reported favourably on it in Sudan kala-azar. They obtained immediate improvement in twenty-four out of twenty-eight cases, but were only able to follow up four cases for 4 months: these did not relapse. Their total dosage varied from 750 mg. to 4·9 grammes, and they were trending towards a relatively intensive course of 100 mg. daily for 15 days, followed by a similar course after a week's interval: total dosage, 3 grammes, or about 60 mg. per kg. They do not specifically mention relapses, but recount exacerbations of fever on commencing new courses. Amongst complications they had syncopal attacks with coma (twice) and also breathlessness, giddiness, and vomiting.

The drug is not very soluble but 10 mg. can be dissolved in 1 c.c. of distilled water. It is given intravenously.

Results.—Fourteen cases were treated with this drug. No absolutely definite scheme of dosage was used but about 1 to 1·3 grammes in twelve injections spread over 14 to 30 days. Of the fourteen cases, seven were cured (three of these had had previous tartar emetic treatment), one of these relapsing once and needing a second course. Courses of treatment in successful cases varied between 1·07 grammes in twelve days and 1·18 grammes in 29 days: the only intensive course used, 2·5 grammes in 14 days.

In the seven cases not cured, several courses were tried on some and there were in all eleven relapses and twice no response to the drug. Response to diamidino stilbene is slower than to urea stibamine, the temperature becoming normal between 2 and 32 days after starting treatment, with an average of 12¼ days.

The relatively unsuccessful results with this drug are in all probability due to inadequate dosage and inadequate intensity of therapy The reasons for this are mechanical, in that diamidino stilbene is not very soluble, 100 mg in 10 c.c. and that suitable syringes holding more than 10 c.c. are difficult to obtain medical, in that the drug has some unpleasant effects, which are set out in detail in the next paragraph The only case treated intensively with a course of 50 mg , 100 mg 150 mg and 200 mg daily to 2 5 grammes, recovered without relapse, and it is hoped to try this type of course further if a new epidemic occurs

Toxicity —Unpleasant sensations of tightness in the chest, of fire pouring through the veins or of great depression occurred in about one-third of the cases. Vomiting only occurred once. It has already been mentioned that the drug was suspected, probably without justification, of causing dental trouble. In one case collapse occurred which was found on careful investigation to be due to an extreme drop in blood pressure (110/75 to 60/0) associated with a very slow pulse, and relieved by adrenaline Use of the drug had to be abandoned

These do not sound very serious, but contrasted with the apparent innocuousness of urea stibamine they do not encourage use of the drug in seriously ill patients.

Summary of Cases treated by Diamidino Stilbene

1 Skin scraping positive (later) Relapse after tartar emetic 26 grains

(*a*) Diamidino stilbene 970 mg in sixteen daily injections afebrile after 5 days No reactions Spleen unaltered Relapsed 16 days after course. Relapsed after course urea stibamine.

(*b*) Diamidino stilbene 1 10 grammes in twelve injections in 32 days Exacerbation at first with expansion of spleen. Temperature down after 24 days Spleen shrank from 6F + to 1F − by end of course Relapsed 45 days after course Spleen up to 5F +

(*c*) Diamidino stilbene 1 30 grammes in thirteen injections in 15 days Temperature down in 4 days. Spleen 4F + Relapsed 43 days after course Spleen 7F +

(*d*) Diamidino stilbene 1 31 grammes in fourteen injections In 43 days Intermittent fever through and after course Spleen remained huge well beyond umbilicus Later cured by intensive urea-stibamine

2 Spleen puncture positive Relapse after tartar emetic, 28½ grains

(*a*) Diamidino stilbene 660 mg. in twelve injections in 15 days Very ill with oedema and spleen beyond umbilicus (7F +) Temperature normal after 10 days spleen 5F + Relapse after 5 days no treatment recommenced.

(*b*) Diamidino stilbene 1 17 grammes in thirteen injections in 30 days Temperature normal in 9 days Spleen very painful at first, down to 3F + at end of course Oedema of feet also disappeared. Dermal leishmanoid (positive) appeared during course 4 months later the skin rash, after developing an amazing verrucosity had dropped off spleen still 3F + no relapse

3 Spleen puncture positive Relapse after tartar emetic 25½ grains Diamidino stilbene 1 20 grammes in thirteen daily injections temperature down in 11 days. Spleen shrank from 8F + to 5F + oedema of the feet disappeared. 2 months later spleen 1F − No relapse in 3 months.

4 Spleen puncture positive Relapse after tartar emetic, 25 grains

(*a*) Diamidino stilbene 990 mg in fifteen daily injections temperature to normal in 10 days Spleen 6F + down to 3F + by end of course. Relapse after 38 days Spleen enormous 8F +

20.2.42. Afebrile spleen 1F + only
24.3.42. W.B.C. 3,200
14.4.42. No fever for 53 days. Sent to convalescent camp
24.4.42. Readmitted with fever 101 to 102 F. and spleen below umbilicus, 7F +
30.4.42 to 23.5.42. Diamadino stilbene 1.13 grammes. Apyrexial 18.5.42.
6.6.42. Spleen 3F + liver 2F + W.B.C. 6,200
8.7.42. Relapse, spleen 6F +
20.7.42 to 23.9.42. Urea stibamine 2.15 grammes. 16.9.42 apyrexial, dermal leishmanoid.
2.10.42. Low fever again.
15.10.42 to 9.11.42. Anthiomaline 66 c.c. 22.10.42 afebrile. 1.11.42 spleen 2F — 10.1.43 spleen 1F — W.B.C. 5,800
20.4.43. Spleen not palpable. Well and fit. 6 months without relapse.

B. CRITERIA OF CURE.

Fever.—This is the most obvious and important. No stretch of the imagination could say that a patient was cured until his fever ceased. But the paragraph on relapses shows that a minimum afebrile period, after ceasing treatment, of 2 to 3 months is necessary before cure can be assumed.

General Condition.—This is of considerable value. If a patient gains weight rapidly and looks well and feels well, he is less likely to relapse than one who in spite of apparent cure "hangs fire."

Spleen.—Unless there is a definite reduction in size of the spleen during the course, followed by progressive diminution afterwards, if still palpable, relapse may be confidently expected. As already mentioned, only two cases showed enlargement more than 1F — on discharge.

Blood Count.—While the white blood count improves with treatment, study of the figures given in an earlier section shows that this is not sudden and dramatic. The white count unless taken under similar conditions each time varies irregularly and in Africans never reaches the figures regarded as standard for Europeans. An improved white count is, therefore, merely a confirmation that the case has improved. Curiously enough the haemoglobin and R.B.C. are of more value in following the prognosis of the case. If these do not rise to adequate figures (70 per cent. Hb and 4,000,000 R.B.C.) it is possible that the infection is latent and a relapse is possible.

Parasites.—Disappearance of the parasites from the tissues is a necessary condition to be satisfied before cure is pronounced. But in most early cases parasites are scanty and difficult to find anyhow and soon disappear on treatment. When dermal leishmanoids appear it is necessary to ensure that skin scrapings are negative before discharge for the parasites appear to persist here longer than elsewhere.

Summary.

As criteria of cure, there must have been no fever for 3 months, the patient must be well and fit and have gained weight, his spleen must have shrunk to not more than 1F — and his blood count have improved, while parasites should not be demonstrable anywhere.

VII Summary

An account is given of 60 cases of kala azar admitted to a military hospital in East Africa. The epidemiology, clinical features, complications, and post-mortem findings are described. The treatment and criteria of cure are discussed, and the success of urea stibamine in adequate dosage is emphasized.

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CUTANEOUS LEISHMANIASIS IN NIGERIA

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Nigeria is included in the geographical distribution of cutaneous leishmaniasis by CRAIG and FAUST (1937) and MANSON-BAHR (1940) but for many years there has been considerable local doubt as to its existence

SMITH (1932) mentions that positive findings have been reported occasionally in Northern Nigeria though in a later publication (1939) he states that the disease has not yet been proved to occur in Nigeria On the other hand MCCULLOCH (1928) asserts that cutaneous leishmaniasis is definitely established in Northern Nigeria and that sections are the only safe method of diagnosis. It is to be regretted that he does not mention the number of cases proved by finding the parasite as this is the only reference we have been able to find confirming its occurrence in this country

The *Annual Reports of the Medical and Health Services of Nigeria* for the years 1924 to 1941 record 131 cases of cutaneous leishmaniasis and five cases

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of kala azar but there is no mention of positive laboratory findings during this period and it is safe to assume that in the majority the diagnosis was solely on clinical grounds.

McCULLOCH (1930) was in charge of the pathological laboratory at Kaduna, Northern Nigeria, during 1929 but his report contains no reference to cutaneous leishmaniasis, nor do those of his predecessors and successors. This laboratory served the whole of the Northern Provinces for many years.

One of us (R. N. H.) had observed clinically suspicious cases at Sokoto, Northern Nigeria, in 1930 but was unable to confirm the diagnosis microscopically. Further attempts over a number of years at Kano were also unsuccessful but in 1942 leishmania were found in smears from a cutaneous sore by the African Technical Assistant at the City Hospital Mr S. ENO. Fourteen cases were diagnosed microscopically during that year but the record of them was unfortunately lost and it was decided to send smears from subsequent cases to the Medical Research Institute for confirmation. This was done and up to the time of writing ten confirmed cases have been seen at Kano during 1943.

CASES.

Case 1.—A European male on leave from Maradi in French Niger Colony reported with multiple ulcers on one leg which he said had commenced as small boils a month previously.

Case 2.—A European male also from Maradi, had multiple papules on his arms and legs of 1 month's duration.

Case 3.—An African male a native of Southern Nigeria but living in Kano, had typical lesions on the thigh with a 4 weeks history.

Case 4.—A Tripolitanian Arab male living in Kano who had papules and ulcers on both legs.

Case 5.—A European male from Zaria in Northern Nigeria where he might have become infected. He had indolent ulcers on the legs of 3 months' duration.

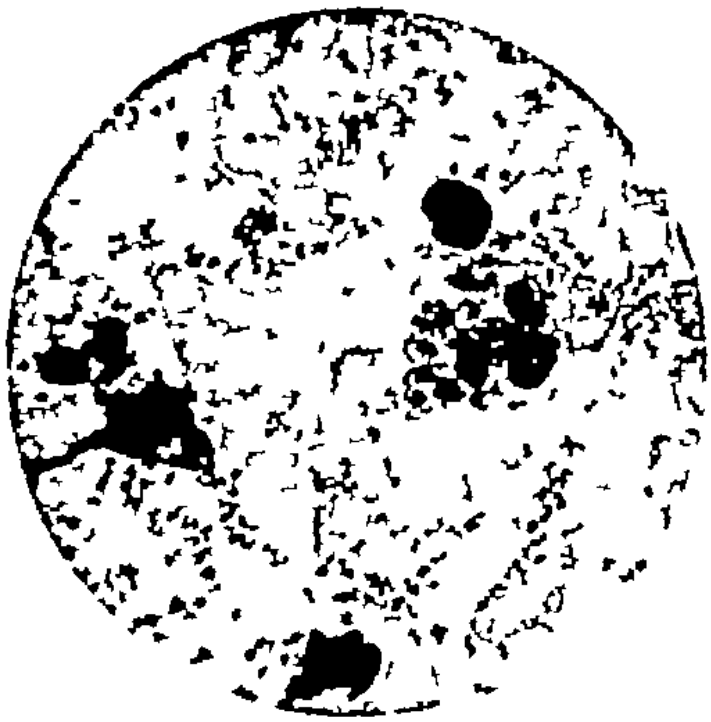
Case 6.—An African female from Sokoto, Northern Nigeria, who had been in Kano for a year. She had extensive ulceration of the right breast and numerous fusiform bacilli were found in the smears as well as leishmania. The case was probably tropical ulcerating phagedaena superimposed on cutaneous leishmaniasis. The disease was stated to be of 6 months' duration.

Cases 7, 8 and 9.—African males natives of Kano who had single lesions on the arm.

Case 10.—An African male native of Kano with an indolent ulcer of the leg.

In all the cases the lesions conformed with the textbook description of oriental sore and they responded well to treatment with tartar emetic. The parasites found in smears stained by Leishman's stain were typical of *Leishmania tropica* and exhibited the range in size and shape associated with this species. A seasonal incidence, towards the end of the rains, has been noted. The species of sandfly occurring in this area of Nigeria have not yet been identified. Kano is situated about 12° N. 8·5° E., and Maradi lies some 150 miles to the north-west. The French Medical Officer there Dr. D. VERGEZ, in a personal communication, states that cutaneous leishmaniasis is not uncommon in his district. In Southern Nigeria whose geographical boundaries are approximately 4° to 9° N. and 3° to 11° E., cutaneous leishmaniasis has not yet been proved to

CASE 3



Photomicrograph of smear from ulcerated nodule showing *Leishmania tropica* × 870

CASE 8

Extensive ulceration of the right breast. Numerous fusiform bacilli in the smears as well as leishmania

occur though many suspicious lesions have been examined at the Medical Research Institute over a number of years It is interesting to note that in the French Cameroons twenty cases were confirmed in 1935 and 1936 by HERVÉ (1937) He states that they occurred in the southern part of the territory which adjoins the eastern boundary of Southern Nigeria

His observations should stimulate further search for the parasite in our Southern Provinces.

SUMMARY

The occurrence of cutaneous leishmaniasis in Nigeria is noted. Ten cases affecting both Africans and Europeans were confirmed by finding the parasite Eight occurred in the northern part of the territory and two came from Maradi in French Niger Colony

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ABDOMINAL PAIN IN THE DIAGNOSIS OF EARLY KALA-AZAR.

BY

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COLE, COSGROVE and ROBINSON (1942) have recorded a very interesting series of cases of kala azar in a battalion of the King's African Rifles. In their report they state "since all were under medical care from the outset a more accurate picture of the disease can be obtained than would be possible from the study of sporadic cases entering civil hospitals." This is very true for unless a number of cases can be under observation from the very beginning *of their illness and later followed up over a long period (which is not possible* in civil hospital practice as a rule—especially the following up part), certain inconsistencies in the usual description of kala-azar are bound to be missed. What particularly interests me is the report of abdominal pain in fourteen cases of the series COLE and his fellow workers quote, five of them vomiting. The literature I have searched so far (including among other works the 11th edition of *Manson's Tropical Diseases* (1940) and even NAPIER'S *Kala Azar* (1927) has contained no reference to this interesting and to my mind diagnostic, symptom of early or insidious kala azar—especially in known endemic areas, such as the District wherein I have been resident for many years. I may say that this early symptom has been the *only* evidence of what has later turned out to be definite kala-azar in some hundreds of cases

in my experience over the past 17 years, during which period some 7,000 odd cases of the disease in all its stages, have been through the fourteen tea estate hospitals under my supervision. Conditions and facilities for observation of cases from the onset, as well as a long follow-up are ideal in this tea-garden type of practice. The local coolie population of approximately 25,000—until very recent years—has been settled for quite a few generations (in the case of most families) and because of this no difficulties whatever are experienced in tracing any case and its history. Therefore, observation of this symptom of abdominal pain (now locally accepted from my own experience as a definitely early one in some cases) has been far from "sporadic" or casual. It is now easily recognized by my assistants and, when noted, the patient is accordingly put on the "suspected" or "observation" list, and, with very rare exceptions about 6 to 9 weeks later other more easily recognized signs or symptoms usually appear. Although several cases of kala azar pass through Assam or Calcutta civil hospitals this symptom has not, to my knowledge, been reported, and doubtless for the reasons mentioned by COLE and his colleagues quoted above. It certainly is seen in the local hospitals—in about 2 per cent. of the total number of kala-azar cases—and perhaps the following general account may prove of interest:—

A TYPICAL CASE HISTORY

On admission the patient usually complains of pain in the abdomen—chiefly epigastric. Pain very severe sometimes. May or may not be accompanied by vomiting or nausea. Vomiting may be only occasional or frequent during the day. There is usually a past history of this abdominal pain, with diarrhœa and indigestion, during attendance at the out patients' clinic some weeks or months previously. Patient returns owing to increase in pain. Diarrhœa still present. Indigestion worse. In the cases with a vomiting history as well it is usually after food and the patient is thinner owing to the inability to take much nourishment without vomiting. In bad cases the fear of vomiting causes anorexia. There is often no other complaint than the associated diarrhœa or indigestion, and there are no physical signs of any sort to guide one at this early stage. In some cases the appetite is good, but if vomiting persists as well as the pain it is lost as just stated. The tongue is usually very clean. The pain is spasmodic, by night as well as by day but chiefly after meals, and lasts from a few seconds to several hours at times. No anti peristalsis or reflex spasmodic lumps are seen or felt in the epigastrium. Pressure on palpation increases pain. Palliative drug treatment and even gastric lavage are of little avail. If one is inexperienced the case is very likely to be labelled "idiopathic gastritis" or "gastralgia of unknown origin," etc. Diagnosis is difficult and is perforce by careful clinical observation, as, apart from this and very minor laboratory facilities, no X ray or postmortem facilities exist in tea estate practice.

An aldehyde or Chopra's test may have been negative when the patient was first admitted from the out-patients department. No splenic puncture is

possible as no enlargement of this organ or of the liver is present A moderate leucopenia may or may not be present. The progress of such a case is of three different kinds *viz* (*a*) The patient may die before a correct diagnosis is made owing to exhaustion and emaciation due to inability to eat on account of persistent pain. (*b*) The pain may spontaneously disappear after a week or so of palliative treatment but not *because* of it, and the patient is discharged "cured of his gastralgia,' etc. only to return some weeks or a few months later and may be diagnosed the second time. (*c*) From experienced practice anti kala azar injections of pentavalent antimony are given as a therapeutic test, and the pain disappears speedily—usually after the third injection A presumptive diagnosis of kala azar is then made and a full course of treatment given It has been observed that an aldehyde test definitely negative on admission becomes definitely positive a week or 10 days later This of course depends on the duration of the prodromal stage prior to hospitalization When a proper aldehyde or Chopra test is obtained the diagnosis is then simplified and all is plain sailing But with no such criterion, and other drug treatment being unavailing there remains but the therapeutic test which should be done early So often have such cases occurred that nowadays it is a routine in my district for all vague gastralgia or gastritis cases to receive this empirical anti kala azar treatment, and the upshot is, as stated above (with *rare* exceptions) a therapeutic early diagnosis One further point of interest, in endemic areas at any rate, is the fact that so many of the patients are members of a family others of which have, very often, well-established signs of kala azar or they have relatives who are definitely known to have had the disease As this knowledge would naturally arouse suspicions early and greatly aid the diagnosis in such cases with atypical onset histories (of merely abdominal pain and some diarrhoea) the family history should never be completed without enquiring if kala azar has affected any member Especially should this not be omitted when it is now a well-established fact that family infection with the disease is very common in Assam and other kala azar areas.

COLE and his colleagues on page 30 of their report, give a description of the clinical appearance of their cases which is identical with the Assam picture in all respects or "true to type. This is now the general description to be found in most textbooks of tropical medicine, and my own observations in the same connection have been published in detail elsewhere (BURKE, 1943) and completely agree with the three authors just mentioned The point of difference between their report and mine lies in their description of the fourteen cases of abdominal pain in the series This symptom and the vomiting were not, however the only ones—but were *part* of the whole clinical picture where the onset, in each case (of this series of fourteen) was typical, with accompanying high fever etc. It was the mention of abdominal pain in the series which first caught my eye and stimulated me to record my series of cases having the same symptom but from an entirely different viewpoint of symptomatic significance which it is hoped will prove of interest In passing one notes that,

as regards treatment and choice of drugs, COLE and his colleagues seem to have been singularly unfortunate. The exhaustion of all Bayer supplies of neo-stibosan, solustibosan, so widely favoured pre War has been a great blow to all engaged in anti kala-azar work. I have had to resort to the less favoured urea stibamine neo-stibene, or stiburea. In my notes on kala azar published recently loc. cit., I made an appeal for a British "foolproof" equivalent of the German neo-stibosan—the best drug I had ever used before the War. Recent samples of the Glaxo Laboratories product stibatin promise to be the (British) answer to my plea. It is a pentavalent antimony solution, and capable of either intramuscular or intravenous administration. The makers claim this substance to be as active and as free from toxicity as the German product. I hope to be able to endorse these claims after the personal trial of stibatin (at present proceeding) is completed.

The following case notes will, I think, suffice to illustrate the significance of the early symptom of abdominal pain in kala azar —

CASE.—*Shishula*.—Coolie girl aged 12.

Had severe epigastric pain in November 1942. Attended out-patients clinic for some days and was discharged. Returned on 14th January 1943 because of increase of pain with diarrhoea. Admitted to hospital and kept under observation. Routine aldehyde and Chopra tests negative on admission. There was severe vomiting after food with occasional diarrhoea and complaint of indigestion and great weakness. The patient had become very thin since November 1942. Appetite good and tongue clean, but patient afraid to eat. Nothing else found on careful examination. My assistant, being new first tried gastric palliative treatment with no success. I advised a further blood test 10 days after admission. This time Chopra's test was + and the aldehyde ++ not very definitely conclusive. However urea stibamine was ordered forthwith in view of the typical case history reported. After the third injection of 0·15 gramme the severe pain ceased and also the vomiting. Weakness was, however extreme and no solids could be retained. Emaciation progressed. The diarrhoea had ceased. On 28th January 1943 cough developed—a mild bronchitis. There was no temperature throughout the illness. Urea stibamine was temporarily withheld owing to the bronchitis. On 1st February—only 21 days after admission—dyspnoea occurred and the patient died a few minutes later.

Space does not permit of the recording here of other cases which ended more happily. Indeed, it is hardly necessary as the history is so similar. With reference to the symptomatology of kala-azar MANSON BAHR (1942) says on page 184 of the latest edition of his textbook —

> The onset of the disease may be either gradual or sudden. In the former instance it cannot be diagnosed at all on clinical grounds etc.

By long and careful observation I believe I am in a position to state definitely that the recognition of the significance of the symptom discussed (even though it may be seen only in 2 or 3 per cent. of cases) provides a clue to the diagnosis "on clinical grounds" of those gradual (or *early*) cases referred to by MANSON BAHR. It must be clearly appreciated that it is not my claim that abdominal pain *per se* is a definite sign of kala azar in all cases. There are many typical or acute cases of kala-azar which give no history of abdominal pain at all. To my mind the symptom, as I have described it, of abdominal

pain, some diarrhoea and a suspicious family history all justify—in the absence of proof of any sort to the contrary—a diagnosis of early or insidious kala-azar especially in definitely epidemic or endemic areas. It should be known and borne in mind by all workers in such areas and I consider that the symptom occurs often enough to warrant its inclusion in the future in the ordinary text-books of tropical medicine among the *lesser* known early symptoms of the disease.

To conclude, it may be observed that a reference to the intestinal or gastric pathology of kala azar would suggest that the cause of this abdominal pain is no doubt due to excessive congestion or even actual blocking of the capillaries of the gastric mucosa with leishmania. In cerebral malaria the capillaries become blocked with resultant irritation of the brain and severe headache, and the same occurs in cerebral human trypanosomiasis, so the kala-azar analogy of the cause of gastric pain is surely not unreasonable. Finally there is a similar explanation, in my opinion, for the severe backache which I have often observed in cases of malarial nephritis which so commonly affects children in this District of Mangaldai and elsewhere in Assam. It would be gratifying to have some other colleague's corroboration of my observations in connection with this interesting symptom of early abdominal pain.

Summary

1 Abdominal pain is often diagnostic of early kala azar

2. This symptom, in my experience, occurs in endemic areas in 2 or 3 per cent. of all kala azar cases, and this is often enough in my opinion, to warrant its addition in future to the general description of the *early* symptoms in text books

3 A family history must *always* be taken and is of great value in certain cases, for arriving at a correct and early diagnosis, even with negative laboratory findings.

4 Stibatin, a new British product of pentavalent antimony in solution promises to equal former Bayer kala-azar remedies.

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AN UNUSUAL CASE OF KALA-AZAR SUCCESSFULLY TREATED WITH STILBAMIDINE

BY

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Corporal S P aged 25 of the Greek Army was admitted to hospital on 28th July 1942, with a three months history of lassitude, fever and loss of weight.

He was born on the Greek island of Ikaria. In 1939 he left his home for Samos, to carry out his compulsory military training 1940 found him in Thrace, from whence he went to Albania, serving in the Greco-Italian War In June, 1941 he returned to Ikaria. He left as a fugitive in early September, 1941 It is reasonably certain, therefore, that infection occurred in Ikaria.

On admission. Thin emaciated, dark young man with hollow cheeks, dry hair receding on his forehead, protuberant abdomen He was pale but cheerful Weight 114 lb Urine N.A.D Teeth, throat, and tongue showed no abnormality No enlarged glands were palpable in the axillae, groins or neck. The cardiovascular and central nervous systems showed no abnormality A pleural rub was heard at the right base posteriorly No free fluid was detected in the abdominal cavity The spleen was not palpable. The liver was palpable 3 inches below the right costal margin. The edge was hard but not tender Temperature, 100° F pulse + respirations normal

Ten days later there was no clinical change, except that there seemed to be irregular consolidation of the right base. A 4 hourly temperature, pulse and respiration chart showed a remittent pyrexia fluctuating between 98·6° and 103° F The pulse was normal in relation to the temperature and the respiration rate was not raised. The following investigations had been done to date Repeated blood smears for malaria parasites and spirochaetes were negative. Six stools for amoebae and cysts and *Bilharzia mansoni* were negative. Three blood cultures were sterile. Three serological examinations for typhoid,

* I am extremely grateful to Professor ADLER for his invaluable guidance in the management of this case

paratyphoid A & B abortus, melitensis, and typhus fevers were negative. Haemoglobin 62 per cent. Red blood cells, 3,900 000 White blood cells, 5,200 Polymorphonuclear 60 per cent lymphocytes 38 per cent., mononuclears, 1 per cent. eosinophiles, 1 per cent No primitive white cells were seen. Blood pressure 100/55 Straight X ray of chest showed Right diaphragm raised up to the fourth interspace. Small area of consolidation above diaphragm Left chest normal. No evidence of tuberculosis."

Treatment

One grain of emetine daily for 4 days, was given Stools examined on these days were negative for amoebae and cysts. After the second injection he complained of pain and tenderness in the liver region and this disappeared after the fourth grain of emetine There was no appreciable diminution in the size of the liver and the fever continued remittent. About this time it was observed that there was a tendency—not marked—for the temperature chart to show a double daily rise Also noteworthy especially in view of the prolonged pyrexia, were the patient's general feeling of well-being and his excellent appetite. The formol gel reaction was strongly and instantly positive. Sternal puncture was done and the marrow juice sown on four tubes of Locke blood-agar and in addition 2 c.c. of venous blood was sown on a fifth tube. In all the tubes flagellates of leishmania were found after 9 days.

Two courses of stilbamidine were given with an interval of 17 days between the two courses. In the first course 23 injections were given. Starting with 50 mg daily the dose was increased to 100 mg daily until a total of 2 grammes had been given. In the second course fifteen injections were given Commencing with 50 mg daily the dose was increased to 100 and finally to 150 mg daily until a total of 2 grammes had been given. In both courses together 4 grammes were given Relevant investigations, including the serum proteins, done before during and after are tabulated below

	Formol-gel reaction	Total Protein grammes	Albumin grammes %	Globulin grammes	Alb. Glob. ratio	Haemoglobin %	Total R.B.C.	Total W.B.C.	Polys %	Lymphs %	Blood sedimentation rate mm. in 1 hour	Weight Lbs.
Normal	—	7.20	4.80	2.70	1·7/1	85	5,000,000	6,000	70	25	2–10	
Before treatment	Intensely positive	10.80	2.60	7.82	2/3/1	55	3,320,000	2,200	40	52	120	118
Between courses	Intensely positive	12.00	1.30	11.70	1/11	60	3,710,000	4,400	75	18	140	117
After treatment	Positive after 30 secs	10.60	2.20	7.52	4/7/1	75	4,120,000	8,000	80	20	100	126
Four months after treatment	—	6.72	3.40	3.32	1·4/1	85	4,600,000	8,200	70	21	30	127

* Stilbamidine (M. & B. 744) is 4 4 -diamidino-stilbene dihydrochloride

At the end of the first course the patient felt well had gained 5 lb in weight and his blood picture had improved. The abnormal signs at his right base had gone and this was confirmed by X ray which showed no abnormality with both diaphragms moving well His liver was smaller palpable only 1 inch below the costal margin. His temperature remained down 10 days after the commencement of the course However in view of the grossly abnormal blood protein figures which persisted (the exceptionally high total protein and the distorted albumin globulin ratio) it was decided to give the second course of stilbamidine.

The drug was supplied in powder form in ampoules each containing 1 gramme. The required quantity was weighed out and placed in a small sterile conical flask. About 2 c.c. of anaesthetic ether was added the night before use and the flask lightly stopped with cotton wool to allow evaporation overnight. The addition of ether would not have been necessary had the weighing been done under sterile conditions One hour before administration 20 c.c. of chemically pure sterile water was added to the now dry powder and this was dissolved by carefully rotating the flask The injection was then given intravenously and slowly The vein used invariably thrombosed and towards the end of the first course small veins on the backs of the hand had to be used the injection being given with a hypodermic needle. For this reason the early injections of the second course were given into the more peripheral veins On four occasions some of the solution penetrated the tissues. The patient complained of immediate pain. However in no case did the pain persist for longer than 2 hours and there was no abscess formation Adrenalin was ready for use during injections but was never used. Flushing of the face was noticed several times during the second course when 150 mg doses were given The injections were given 1 hour before the midday meal The patient remained in bed during the treatment. He was given calcium and vitamin preparations by mouth and a liberal diet rich in carbohydrates

The serum protein analyses in this case are of interest because of the high globulin albumin ratio after the first course of treatment, figures which are unusually high even for kala azar Another interesting feature is the fact that at no time during the illness was the spleen palpable.

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ASTHMA PRODUCED BY ASCARIS INFESTATION

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An account of an asthmatic attack that appeared to be directly related to ascaris infestation seems to be sufficiently interesting to merit recording The case occurred at sea on board a ship of the Canadian Merchant Navy the limitations of maritime medicine account for the paucity of laboratory work in connection with the case.

Case History

J M aged 22, negro native of Montserrat British West Indies First seen on the night of 12th April, 1942. At that time he was sitting on the deck outside the sick bay his hands pressed tightly to the deck so as to bring the accessory respiratory muscles into play He was extremely cyanosed, sweating with cold extremities and feeble pulse He was also extremely nervous, alarmed at what was to him a novel experience and was convinced that he was going to die. Whilst I was preparing an adrenalin injection the patient vomited some frothy very bile-stained material, in which were moving three live *Ascaris* worms Unfortunately these were thrown overboard before their sex could be determined. Almost immediately after vomiting the patient experienced great relief and although I gave him the adrenalin injection I think that the symptoms might have cleared up without any medication whatsoever

There was no family history of asthma or any other allergic disease. The patient had lived in Montserrat all his life, with the exception of one trip to St. Kitts and the present voyage, in which he had gone as far as Halifax, Canada. He was positive that this was the first asthmatic attack that he had ever had in his life and gave no history of hay fever or urticaria It was the suddenness and unknown nature of the malady that had caused him to be so terrified when first seen

* I have to thank Dr H. H BAYLEY of St. Michael Barbados for the laboratory work performed in connection with the above investigation and also for kindly supplying me with ascaris antigen.